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## Impact of Major Depressive Disorder on Comorbidities: A Systematic Literature Review

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### ABSTRACT

**Objective:** To summarize the breadth of data exploring the relationship between major depressive disorder (MDD) and both the incidence and the disease course of a range of comorbidities.

**Data Sources:** The authors searched MEDLINE, Embase, PsycINFO, Cochrane Database of Systematic Reviews, and several prespecified congresses. Searches included terms related to MDD and several comorbidity categories, restricted to those published in the English language from 2005 onward.

**Study Selection:** Eligibility criteria included observational studies within North America and Europe that examined the covariate-adjusted impact of MDD on the risk and/or severity of comorbidities. A total of 6,811 articles were initially identified for screening.

**Data Extraction:** Two investigators extracted data and assessed study quality.

**Results:** In total, 199 articles were included. Depression was significantly ( $P < .05$ ) associated with an increased incidence of dementia and Alzheimer's disease as well as cognitive decline in individuals with existing disease; increased incidence and worsening of cardiovascular disease/events (although mixed results were found for stroke); worsening of metabolic syndrome; increased incidence of diabetes, particularly among men, and worsening of existing diabetes; increased incidence of obesity, particularly among women; increased incidence and worsening of certain autoimmune diseases; increased incidence and severity of HIV/AIDS; and increased incidence of drug abuse and severity of both alcohol and drug abuse.

**Conclusions:** The presence of MDD was identified as a risk factor for both the development and the worsening of a range of comorbidities. These results highlight the importance of addressing depression early in its course and the need for integrating mental and general health care.

*J Clin Psychiatry* 2022;83(6):21r14328

**To cite:** Arnaud AM, Brister TS, Duckworth K, et al. Impact of major depressive disorder on comorbidities: a systematic literature review. *J Clin Psychiatry*. 2022;83(6):21r14328.

**To share:** <https://doi.org/10.4088/JCP.21r14328>

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Major depressive disorder (MDD) is defined as a depressed mood and/or loss of interest or pleasure in daily activities along with symptoms such as weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness, diminished ability to think or concentrate, and thoughts of death or suicidal ideation (minimum 5 symptoms total), which have collectively been present during the same 2-week period and represent a change from previous functioning.<sup>1</sup> The episode is considered MDD if it is not attributable to the physiologic effects of a substance or not better explained by another medical condition (such as schizophrenia) and a manic episode or a hypomanic episode has never been observed.<sup>1</sup> MDD affects over 160 million people globally<sup>2</sup> and is one of the most common mental health disorders in several countries. Notably, depression is recognized by the World Health Organization (WHO) as a major contributor to the overall global burden of disease.<sup>3</sup>

Complicating our understanding of MDD and its treatment is the presence of several physical and psychological comorbidities among individuals with depression, demonstrating an apparent relationship between physical and mental health. The interaction between depression and many of these comorbidities is not fully understood but, in several cases, appears to be complex and potentially bidirectional. The presence of comorbidities adds to both the humanistic and the economic burden associated with depression; notably, 63% of total MDD-associated costs in the United States in 2018 were attributed to an increased cost of treating comorbid conditions rather than to MDD itself.<sup>4,5</sup> Furthermore, individuals with MDD have been shown to have a decreased life expectancy compared with those without depression<sup>6</sup>; it is therefore possible that the worsening of associated comorbidities could be a contributing factor to earlier mortality.

Although the associations between depression and several comorbidities have been studied individually, not all have been explored systematically. The objective of this review was to qualitatively identify and summarize the breadth of observational data that examine the potential causality of MDD on multiple comorbidities, including the risk of developing new diseases and the impact on the disease course of preexisting comorbidities. Of note, this review explores several comorbidity categories simultaneously to provide a broader illustration of the collective comorbidity risks among people with depression.

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### Clinical Points

- Although there are many well-studied comorbidities among people with depression, a broader illustration of how the risk and severity of several comorbidities across different disease areas are simultaneously impacted by the presence of depression is less clear.
- Providers should ensure that people have appropriate access to screening, diagnosis, and adequate treatment not only for depression, but also for the comorbidities that could be impacted by depression.

## METHODS

A systematic literature search for studies that examined the association between MDD and comorbidities was conducted with methods consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.<sup>7</sup>

Categories of comorbidities were first determined from preliminary literature research, review of national agency and patients' advocacy group reports, review of US medical claims data, and expert opinion. The final list of comorbidity categories included cancer, central nervous system (CNS) disorders, cardiovascular disease (CVD), metabolic and endocrine diseases, autoimmune and gastrointestinal (GI) diseases, pain-related conditions, respiratory disorders, and substance abuse disorders. This review focused on comorbidities related to physical and substance abuse disorders; anxiety and other psychiatric disorders were not included.

Databases searched included Embase, MEDLINE (including MEDLINE In-Process), Cochrane Database of Systematic Reviews, and PsycINFO, and the search used terms for MDD, comorbidity categories, and observational studies (the full search strategy is provided in Supplementary Table 1). In addition, abstracts from several relevant congresses were reviewed and hand searches of referenced publications were undertaken. Searches were conducted in November 2019 and were restricted to the previous 15 years for database searches and the previous 2 years for conference proceedings.

Included studies assessed the relationship between MDD and comorbidities and were required to use a covariate-adjusted analysis to identify the association of MDD with downstream comorbidities (affecting either the risk of developing a comorbidity or the disease course of an existing comorbidity). Geographically, included studies were restricted to those undertaken in Europe and North America. Covariate-adjusted analyses included those adjusted for at least one relevant covariate to minimize their impact on the association with depression and the comorbidity; examples include demographics such as age and sex, other diseases, and behaviors such as smoking and alcohol consumption. Studies that assessed only associations in the opposite direction (ie, the impact of comorbidities on the development or disease

course of depression) were excluded. Included studies were required to be observational in design (including meta-analyses of observational data), and only English-language records were searched; a complete list of criteria is provided in Supplementary Table 2. Although the aim of this review was to identify studies of people with MDD, the heterogeneous way that these individuals are described and identified in scientific literature (such as through symptom rating scales or retrospectively from medical records) did not allow for a strict criterion of physician diagnosis of MDD. Indeed, scales and questionnaires are often used in clinical practice to screen, diagnose, and monitor depression. This review therefore included studies of people with MDD or depression otherwise defined by the authors that was not clearly a diagnosis for a different type or severity level of depression (such as dysthymia).

Search results were screened by 2 separate reviewers initially by titles and abstracts, followed by a review of the full text; any disputes were resolved through discussion between reviewers or consultation with a third reviewer. Data from included studies were extracted by 2 independent reviewers, and any discrepancies between extractions were verified for accuracy by an independent third reviewer. Data describing the study methodology, participant demographic and clinical characteristics, and associations between MDD and comorbidities were extracted. The quality of included studies was assessed by reviewers using the Newcastle-Ottawa Scale for observational studies and the checklist recommended by the National Institute for Health and Care Excellence (NICE) for meta-analyses (see Supplementary Tables 3–6).<sup>8,9</sup>

## RESULTS

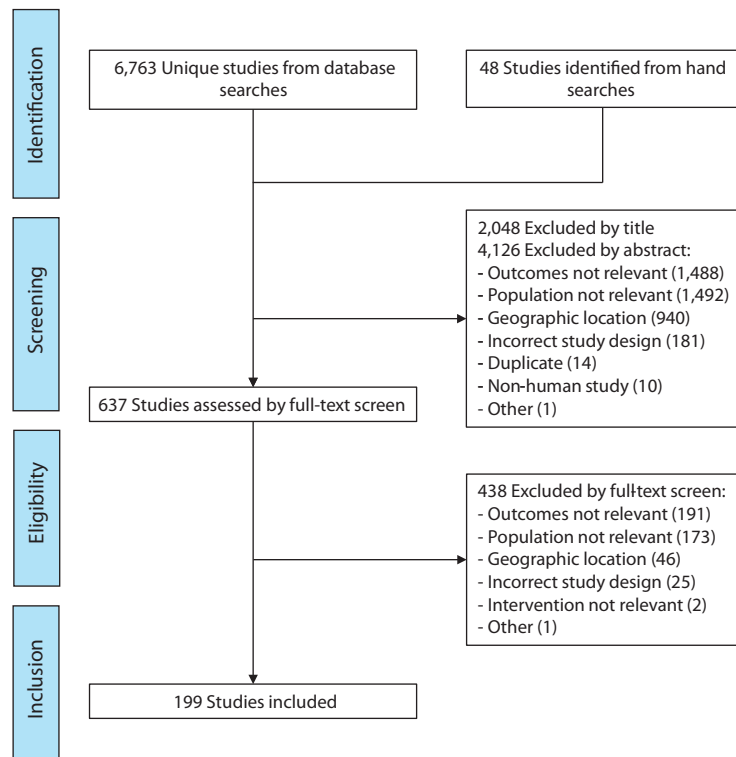
A total of 6,763 articles were identified by database searches for initial screening, and these were combined with another 48 relevant articles identified from conference abstracts and hand searches of references lists from other reviews. Overall, 199 articles met the inclusion criteria (Figure 1); these included 142 cohort studies, 15 cross-sectional studies, 15 case-control studies, 26 meta-analyses of observational data, and 1 ancillary study from a clinical trial. Studies ranged broadly in size from fewer than 50 to nearly 5 million participants (see Supplementary Table 7 for a complete list). A summary of the strength of associations found between depression and the incidence and severity of several comorbidities is provided in Figure 2. Findings from all studies are summarized in the following sections; for brevity, comorbidities with findings of note are reported in tables with all other depression-associated outcomes presented in Supplementary Tables 8–31.

### Cancer

A total of 12 observational studies (13 publications) and 2 meta-analyses were identified through this systematic review. One meta-analysis<sup>10</sup> of 32 studies showed that although an analysis of studies that included patients with cancer and depressive symptoms demonstrated a significant association

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Figure 1. PRISMA Figure of Search and Screen



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

between depression and mortality (hazard ratio [HR] = 1.09; 95% confidence interval [CI]: 1.03 to 1.15;  $P = .003$ ), when a clinical depression diagnosis was required this association had a wider confidence interval and statistical significance was no longer demonstrated (HR = 1.67; 95% CI, 0.96 to 2.90;  $P = .07$ ). Furthermore, the meta-analysis also showed no significant association between depressive symptoms and cancer recurrence (risk ratio [RR] = 1.23; 95% CI, 0.85 to 1.77;  $P = .275$ ).<sup>10</sup> Among individual studies identified by this systematic review, we did not find a consistent and significant impact of depression on the new incidence of cancer nor on assessments of cancer severity/mortality of patients with preexisting cancer (see Supplementary Tables 8 and 9 for complete information). For example, in the Baltimore Epidemiologic Catchment Area study<sup>11</sup> that had the longest duration of follow-up of all identified studies (24 years), a lifetime history of major depressive episodes (MDE) was associated with the risk of any incident cancer (adjusted HR = 1.87; 95% CI, 1.16 to 3.01); however, the adjusted analysis lost significance in a subgroup that excluded 145 respondents who rated their health status as poor at baseline.

### CNS Disorders

This review identified a total of 29 observational studies (in 30 publications) and 3 meta-analyses assessing the relationship between depression and CNS disorders. Consistently, depression was demonstrated to be significantly associated with an increased incidence of new dementia

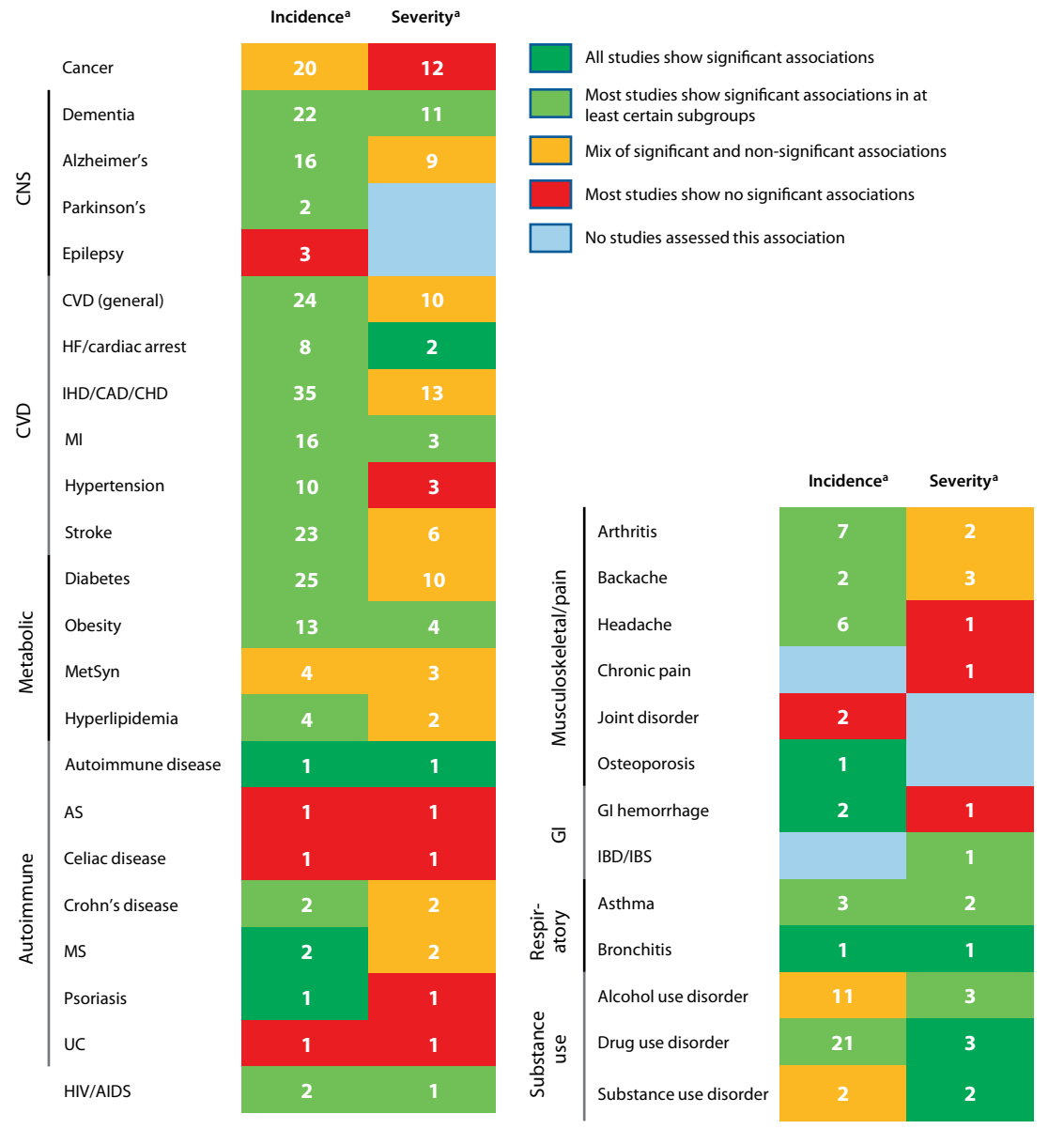
and Alzheimer's disease or cognitive decline in people with existing disease, and with the incidence of Parkinson's disease.

**Incident dementia and Alzheimer's disease.** Two meta-analyses<sup>12,13</sup> (in 23 and 20 studies, respectively) that assessed the association of depression with incident dementia (pooled odds ratio [OR] = 1.96; 95% CI, 1.64 to 2.34;  $P < .0001$ ; 23-study meta-analysis only) and/or Alzheimer's disease (pooled ORs for Alzheimer's disease = 1.85; 95% CI, 1.45 to 2.37;  $P < .0001$  and 1.98; 95% CI, 1.76 to 2.24;  $P < .001$ , respectively) showed significant associations overall and across all subgroups. Among another 22 studies (in 23 publications) identified by the review for this comparison, most showed a significant association between depression and the incidence of dementia and many also showed a significant association between depression and the incidence of Alzheimer's disease (see Supplementary Table 10 for complete information).

**Dementia and Alzheimer's disease severity.** Five studies assessed the impact of depression on the severity of preexisting dementia and/or Alzheimer's disease and nearly all (4 of 5) showed significant and positive associations between presence/severity of depression and cognitive decline/worsening of symptoms in these cohorts (Table 1). Additional details for associations between depression and CNS disorders, including findings in people with epilepsy and Parkinson's disease, can be found in or subsequent to Supplementary Table 10.

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**Figure 2. Summary of Associations Between Depression and Risk of Developing Comorbidities (Incidence) and Whether the Course of Preexisting Comorbidities Is Worsened (Severity)**



<sup>a</sup>Numbers represent the number of studies identified by the review for the specific association. Studies were assessed based on the presence of statistically significant associations between depression and comorbidity risk or severity when controlling for covariates such as demographics to identify potential causality of the downstream impact of MDD on comorbidities separate from other prognostic or risk factors. To reach the threshold for “most studies showed significant associations in at least certain subgroups,” statistically significant associations were required to be observed in ≥ 1 analysis from ≥ 70% of identified studies. If ≥ 50% of studies showed no positive association in any analyses, and two-thirds or more studies reported either no positive association or significant associations only in unadjusted analyses that lost statistical significance upon adjustment, the category was listed as “most studies show no significant associations.” Categories with a mix of results that failed to meet threshold for either significant or no significant associations were classified as having a “mix of significant and nonsignificant associations.”

Abbreviations: AIDS = acquired immunodeficiency syndrome, AS = ankylosing spondylitis, CAD = coronary artery disease, CHD = coronary heart disease, CNS = central nervous system, CVD = cardiovascular disease, GI = gastrointestinal, HF = heart failure, HIV = human immunodeficiency virus, IBD = irritable bowel disease, IBS = irritable bowel syndrome, IHD = ischemic heart disease, MDD = major depressive disorder, MetSyn = metabolic syndrome, MI = myocardial infarction, MS = multiple sclerosis, UC = ulcerative colitis.

**Cardiovascular Disease**

The association between MDD and CVD has been studied widely, and the review identified 67 observational studies and 14 meta-analyses that assessed the association between depression and incidence or worsening of CVD. Most studies identified an association between MDD and the subsequent

incidence or worsening of CVD across several disease categories, including general CVD (or combined endpoints), heart failure, hypertension, ischemic heart disease/coronary artery disease, and myocardial infarction (MI; see Supplementary Tables 11–21 for complete information). In this systematic literature review, measures of disease

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**Table 1. Summary of Studies Assessing the Association Between Depression and Severity of Dementia/Alzheimer's Disease**

Study (N), Design	Depression Definition	Estimate; Period	Impact of Depression on Comorbidity <sup>a</sup>	
			Presence of Depression	Depression Recurrence/Severity <sup>b</sup>
<b>Dementia</b>				
Sawa et al 2014 <sup>14</sup> (N = 39) Retrospective case-control	Medical chart diagnosis	OR (95% CI) presence of dementia symptoms; 2-year data collection <sup>c</sup>	MDD: <b>12.57 (1.31 to 120.74); P = .03</b> Use of antidepressants: <b>6.49 (1.02 to 41.25); P = .047</b>	NR
Wilson et al 2016 <sup>15</sup> (N = 1,965) Prospective cohort	DSM-III MDD criteria assessed using DIS	Regression model estimate ± SE depression to rate of global cognitive decline; mean 8-year follow-up <sup>d</sup>	Cognitive intercept: <b>-0.134 ± 0.030; P &lt; .001</b> Cognitive slope: <b>-0.026 ± 0.007; P &lt; .001</b>	<b>Elevated depressive symptoms<sup>e</sup></b> Cognitive intercept: <b>-0.141 ± 0.033; P &lt; .001</b> Cognitive slope: <b>-0.039 ± 0.009; P &lt; .001</b>
<b>Alzheimer's disease</b>				
Ransom et al 2019 <sup>16</sup> (N = 785) Retrospective cohort	ICD codes	Change in cognition; 4-year data collection	MDD did not contribute meaningfully to prediction of MMSE score change; data NR	NR
Cannon-Spoor et al 2005 <sup>17</sup> (N = 43) Cross-sectional	DSM-III MDD criteria using CADD	Adjusted mean scores of cognitive performance scales with vs without MDD; lifetime history assessed <sup>f</sup>	MMSE: <b>22.9 vs 25.8; P = .002</b> Mattis Initiation/Perseveration: <b>29.6 vs 33.1; P = .007</b> WAIS-R: Full-Scale IQ: <b>95.2 vs 104.5; P = .002</b> Verbal IQ: <b>96.7 vs 107.0; P = .001</b> Performance IQ: 89.5 vs 99.6; P = .06 Buschke: Recall: <b>4.1 vs 5.1; P = .04</b> Consistency: 0.14 vs 0.27; P = .24 Fluency: Letter: <b>28.6 vs 35.4; P = .04</b> Category: 27.4 vs 25.6; P = .52	NR
Wilson et al 2011 <sup>18</sup> (Rush Memory and Aging Project) (N = 785) Prospective cohort	NEO Personality Inventory-Revised	Regression model estimate ± SE depression to rate of global cognitive decline; mean 3.4-year follow-up <sup>d</sup>	NR	<u>Per 1-unit change in depression trait score<sup>g</sup></u> Overall decline: <b>-0.015 ± 0.003; P &lt; .001</b> Episodic memory: <b>-0.003 ± 0.001; P = .045</b> Semantic memory: -0.000 ± 0.001; P = .751 Working memory: -0.003 ± 0.001; P = .059 Perceptual speed: <b>-0.003 ± 0.001; P = .019</b> Visuospatial ability: 0.001 ± 0.002; P = .353

<sup>a</sup>When multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression versus no depression. Statistically significant differences ( $P < .05$ ) are shown in bold;  $P$  values are reported when available.

<sup>b</sup>For the "Depression Recurrence/Severity" category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>c</sup>Adjusted for age and sex.

<sup>d</sup>Adjusted for age, sex, and years of education.

<sup>e</sup>Unclear if dementia population.

<sup>f</sup>Adjusted for age, illness duration, and education level (different analyses adjusted for different factors).

<sup>g</sup>Unclear if population with Alzheimer's disease.

Abbreviations: CADD=Clinical Assessment of Depression in Dementia; DIS=Diagnostic Interview Schedule; DSM-III=Diagnostic and Statistical Manual of Mental Disorders, Third Edition; ICD=International Classification of Diseases; MDD=major depressive disorder; MMSE=Mini-Mental State Examination; NR=not reported; OR=odds ratio; SE=standard error; WAIS-R=Wechsler Adult Intelligence Scale-Revised.

worsening included subsequent cardiovascular events among individuals with prior events/existing chronic CVD as well as cardiac mortality in both the general populations and populations of people with preexisting CVD; the association between depression and these various measures of disease worsening was consistently significant across most analyses (see Supplementary Tables 11–23 for complete information). Among studies that took depression severity into account, these associations often became stronger as depression severity increased (see Supplementary Tables 11–23 for

complete information). Furthermore, studies that assessed the duration of MDD and/or number of MDD episodes also found significant associations between greater durations or episode numbers and ischemic heart disease mortality, incidence of hypertension and heart disease, incidence of major coronary heart disease events, and incidence of acute MI (see Supplementary Tables 14–17 and 20 for complete information).<sup>19–22</sup>

**Stroke incidence and severity.** Of the many CVD categories, the relationship between depression and stroke

incidence had the greatest variability. The review identified 3 meta-analyses (assessing 28 studies [2 meta-analyses each] and 30 studies, respectively), which consistently demonstrated significant associations between depression and incident stroke.<sup>23–25</sup> Findings from the individual studies identified by the review (15 in total), however, were mixed, with some showing a significant association for this relationship and others showing mixed results across different analyses, while another group of studies showed no significant associations (see Supplementary Table 22 for complete information). Among 3 studies and 1 meta-analysis of 6 studies included in this review that assessed the association between depression and stroke severity (generally measured as poststroke function or recovery), the meta-analysis reported a significant association between depression and severe long-term disability among people with stroke (OR = 2.16; 95% CI, 1.70 to 2.77),<sup>26</sup> and results from individual studies generally reflected these findings, with 2 of 3 studies that assessed poststroke function/recovery reporting a greater likelihood of disability in patients with depression (see Supplementary Table 23 for complete information).

**Incident diabetes.** In total, 17 studies (including 2 analyses from metabolic syndrome studies) and 4 meta-analyses assessed the relationship between depression and a subsequent diagnosis of diabetes with follow-up times ranging from 3 to 17 years. The meta-analyses showed a consistently significant association between depression and incident diabetes in the follow-up period both overall and across several subgroup and sensitivity analyses.<sup>27,29,30,45</sup> Six individual study analyses focused on type 2 diabetes only, 1 study each focused on type 1 diabetes and gestational diabetes only, and the remaining studies either did not clarify diabetes type or included both types 1 and 2. Several individual studies reflected the significant associations found in the meta-analyses (either overall or in 1 or more subgroups of participants; Table 2).

Among studies that presented stratified analyses by age and sex, no clear and consistent trends were observed,<sup>32,38,39</sup> although it was notable that a meta-analysis showed a significant association between incident type 2 diabetes in men and depression (RR = 1.57; 95% CI, 1.24 to 1.99), whereas this association was not significant among women (RR = 1.26; 95% CI, 0.95 to 1.67).<sup>45</sup> Three studies evaluated the impact of depression severity on the increased risk of incident diabetes. In one analysis, people with severe depression had greater odds of developing type 2 diabetes compared with those who had no depression (OR = 1.42; 95% CI, 1.01 to 1.99), and at the same time antidepressant use (regardless of depression severity) was also significantly associated with incident diabetes (OR = 2.76; 95% CI, 1.93 to 3.94), suggesting that medication use could be indicative of a unique depression-diabetes association.<sup>37</sup> By contrast, the Zaragoza Dementia and Depression (ZARADEMP) study, which adjusted for antidepressant use as a covariate, found an association between nonsevere depression and incident diabetes (HR = 1.66; 95% CI, 1.01 to 2.75;  $P = .048$ ),

but this did not remain significant in people with severe depression.<sup>33</sup> A separate analysis of the Nurses' Health Study restricted to participants without depression at baseline found that women had a higher risk of developing type 2 diabetes as their depressive symptoms, measured by the 5-item Mental Health Index (MHI-5) score (categorized into 4 groups in order from best to worst mental health: 86–100 [reference case], 76–85, 53–75, and 52 or lower), worsened over time to 53–75 compared with those who had scores that remained between 86 and 100 (RR = 1.13; 95% CI, 1.02 to 1.26), but this association was no longer significant when scores decreased to a threshold of 52 and below, which was considered "depressed mood."<sup>41</sup>

**Diabetes severity.** Six studies, including 3 separate analyses of the Pathways Epidemiologic Study, assessed the association between depression and diabetes severity (type 2 diabetes only in 5 of 6 studies; 1 study included both type 1 and type 2 diabetes). A consistent association between presence/severity of depression with diabetes severity, measured by glycemic control, macrovascular and microvascular events, and diabetic retinopathy, was demonstrated across most analyses, with all 6 studies reporting at least one positive association between depression and diabetes severity (see Supplementary Table 25 for complete information).

**Incident metabolic syndrome.** The association between depression and a subsequent diagnosis of metabolic syndrome was reported in 3 studies. In general, most analyses did not show a significant association between depression presence or recurrence and the incidence of metabolic syndrome. In one exception, a subgroup of men in the cross-sectional Study of Health In Pomerania (SHIP-0; but not the similar SHIP-TREND-0) study had a significant association between a history of depression at the syndromal level and metabolic syndrome (OR = 1.53; 95% CI, 1.06 to 2.21;  $P \leq .05$ ), but other subgroups of men (those with lifetime MDD and those from the SHIP-TREND-0 study) and all parallel subgroups of women did not report similar findings.<sup>43</sup> People with recurrent depression in the Study of Women's Health Across the Nation (SWAN) study also demonstrated nonsignificant associations between history of or current MDE as a predictor of metabolic syndrome (HR = 1.83; 95% CI, 0.99 to 4.76), and when this was no longer restricted to recurrent depression only the association weakened further (HR = 1.54; 95% CI, 0.93 to 3.40).<sup>44</sup> In the prospective Cohorte Lausannoise (CoLaus)/Psychiatric arm of the CoLaus Study (PsyCoLaus) population cohort that assessed the relationship by MDD subtypes, only atypical MDD (OR = 2.49; 95% CI, 1.30 to 4.77;  $P < .01$ ), and not melancholic (OR = 1.45; 95% CI, 0.78 to 2.69) or unspecified MDD (OR = 1.44; 95% CI, 0.83 to 2.49), was associated with incident metabolic syndrome over approximately 5 years.<sup>46</sup>

**Incident obesity.** The review identified 10 studies (including 2 analyses of abdominal obesity from metabolic syndrome studies) and 2 meta-analyses that assessed the association between depression and incident obesity (see

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**Table 2. Summary of Studies Assessing the Association Between Depression and Diabetes Incidence**

Study (N), Design	Depression Definition	Estimate; Time Period	Impact of Depression on Comorbidity <sup>a</sup>	
			Presence of Depression	Depression Recurrence/Severity <sup>b</sup>
<b>Diabetes Only</b>				
Atasoy et al 2018 <sup>31</sup> (MONICA/ KORA) (N=9,340) Prospective cohort	DEEX score ≥ 10/12, men/women	HR (95% CI) for developing T2DM; mean 15.4-year follow-up <sup>c</sup>	Overall: <b>1.16 (1.06 to 1.02); P = .02</b> Normal weight, depressed: 1.30 (0.90 to 1.91) Overweight: <b>3.11 (2.30 to 4.21); P &lt; .0001</b> Obese: <b>8.05 (5.90 to 10.98); P &lt; .0001</b>	NR
Brown et al 2005 <sup>32</sup> (N=9,340) Retrospective case-control	ICD codes	OR (95% CI) history of depression and incident T2DM; 3-year exposure period <sup>d</sup>	Overall: <b>1.47 (1.14 to 1.90); P = .002</b> Age 20–50 years: <b>1.23 (1.10 to 1.37)</b> Age ≥ 51 years: 0.92 (0.84 to 1.00)	NR
Campayo et al 2010 <sup>33</sup> (ZARADEMP) (N=3,521) Prospective cohort	GMS-AGECAT (details NR)	HR (95% CI) depression as predictor of diabetes; 5-year follow-up <sup>e</sup>	Overall: <b>1.65 (1.02 to 2.66); P = .04</b> First episode: 1.59 (0.96 to 2.64); P = .07 Baseline only: 1.43 (0.79 to 2.58); P = .24 Untreated: <b>1.83 (1.11 to 2.99); P = .02</b> Treated: 0.823 (0.23 to 2.98); P = .77	Nonsevere: <b>1.66 (1.01 to 2.75); P = .048</b> Severe: 1.57 (0.55 to 4.44); P = .39 Previous episode: 2.06 (0.73 to 5.79); P = .17 Baseline + follow-up: <b>2.09 (1.06 to 4.14); P = .03</b>
Eriksson et al 2008 <sup>34</sup> (Stockholm Diabetes Prevention Program) (N=5,227) Prospective cohort	Patient questionnaire	OR (95% CI) depression quartile at baseline (low, middle, and high) and T2DM at 8- to 10-year follow-up <sup>f</sup>	NR	<u>Men</u> Middle vs low: 1.3 (1.0 to 1.7) High vs low: 1.6 (0.6 to 4.3) <u>Women</u> Middle vs low: 1.0 (0.7 to 1.3) High vs low: 0.7 (0.3 to 1.6)
Farmer et al 2008 <sup>35</sup> (N=2,430) Retrospective case-control	DSM-IV or ICD recurrent MDD criteria using SCAN 2.1	OR (95% CI) for T2DM in cases with recurrent depression vs controls; lifetime history assessed <sup>g</sup>	NR	2.06 (0.84 to 5.04); P = NS
Karakus and Patton 2011 <sup>36</sup> (Health and Retirement Study) (N=3,645) Prospective cohort	8-item CES-D score ≥ 3	OR (95% CI) depression at baseline as predictor of diabetes; 12-year follow-up <sup>h</sup>	Overall: <b>1.50 (1.01 to 2.24); P = .04</b> Including excessive alcohol drinking: <b>1.505; P = .044</b>	NR
Kivimäki et al 2010 <sup>37</sup> (N=59,940) Retrospective case-control	ICD codes	Study 1: OR (95% CI) for incident T2DM, depression vs no depression; 4-year follow-up <sup>i</sup> Study 2: HR (95% CI) for incident T2DM associated with antidepressant use; mean 4.75-year follow-up <sup>i</sup>	Untreated: 1.05 (0.55 to 2.04) Antidepressant use: <b>2.76 (1.93 to 3.94)</b>  200–399 defined daily doses/year: <b>1.53 (1.25 to 1.87)</b> ≥ 400 defined daily doses/year: <b>2.00 (1.51 to 2.66)</b> <b>P trend &lt; .0001</b>	Severe: <b>1.42 (1.01 to 1.99)</b>  NR
Mallon et al 2005 <sup>38</sup> (N=1,187) Prospective cohort	Self-report	RR (95% CI) new diabetes according to depression at baseline; 12-year follow-up <sup>j</sup>	Women: 1.0 (0.3 to 3.2)/0.9 (0.3 to 2.9) Men: 0.6 (0.2 to 2.0)/1.3 (0.4 to 3.6) <sup>k</sup>	NR
Mezuk et al 2008a <sup>28</sup> (Baltimore ECA) (N=3,481) Prospective cohort	DIS; details NR	HR (95% CI) risk of T2DM according to lifetime MDD; 24-year follow-up <sup>l</sup>	1981–2005: <b>1.62 (1.03 to 2.55); P &lt; .05</b> 1993–2005: <b>2.04 (1.09 to 3.81); P &lt; .05</b>	NR
Mezuk et al 2015 <sup>39</sup> (SALT) (N=37,043) Cross-sectional	DSM-IV MDD using CIDI-SF	HR (95% CI) lifetime MDD predicting T2DM; 4-year follow-up <sup>m</sup>	Overall: 1.07 (0.91 to 1.26) <u>Age 40–55 years</u> All: 1.32 (1.00 to 1.80) Women: <b>1.74 (1.09 to 2.79)</b> Men: 1.08 (0.70 to 1.67) <u>Age ≥ 55 years</u> All: 1.00 (0.83 to 1.21) Women: 0.92 (0.72 to 1.18) Men: 1.17 (0.87 to 1.57)	NR
Nichols and Moler 2011 <sup>40</sup> (N=58,056) Retrospective cohort	ICD codes	RR (95% CI) risk of T2DM according to depression; follow-up ≤ 5 years <sup>n</sup>	<b>1.10 (1.02 to 1.20)</b>	NR
Pan et al 2010 <sup>41</sup> (Nurses' Health Study) (N=65,381) Prospective cohort	Self-report; MHI-5 score ≤ 52 or with clinical depression	RR (95% CI) incident T2DM according to depressive symptom status; 10-year follow-up <sup>o</sup>	Any depressed mood: <b>1.17 (1.05 to 1.30)</b> Physician-diagnosed, untreated: 1.05 (0.85 to 1.30) Physician-diagnosed, with antidepressants: <b>1.25 (1.10 to 1.41)</b>	<u>By MHI-5 score</u> 86–100: reference 76–85: 1.07 (0.97 to 1.17) 53–75: <b>1.13 (1.02 to 1.26); P trend = .002</b> ≤ 52: 1.04 (0.83 to 1.31)

(continued)

**Table 2 (continued). Summary of Studies Assessing the Association Between Depression and Diabetes Incidence**

Study (N), Design	Depression Definition	Estimate; Time Period	Impact of Depression on Comorbidity <sup>a</sup>	
			Presence of Depression	Depression Recurrence/Severity <sup>b</sup>
Windle and Windle 2013 <sup>42</sup> (N = 557) Prospective cohort	DSM-IV MDD criteria using CIDI	OR (95% CI) lifetime MDD predicting T2DM; 5-year follow-up <sup>p</sup>	Single MDD: 0.5 (0.13 to 1.88)	Recurrent MDD: <b>3.20 (1.10 to 9.33); P &lt; .05</b>
<b>Diabetes as a Component of Metabolic Syndrome</b>				
Block et al 2016 <sup>43</sup> (SHIP-0; SHIP-TREND-0) (N = 8,040) Cross-sectional	DSM-IV MDD criteria using CID-S or M-CIDI	OR (95% CI) MDD and elevated glucose or antidiabetic medication; 4-year follow-up <sup>q</sup>	<u>Women</u> SHIP-0: 1.49 (0.92 to 2.41) SHIP-TREND-0: 0.96 (0.70 to 1.32) MDD lifetime: 0.85 (0.58 to 1.23) <u>Men</u> SHIP-0: 0.94 (0.50 to 1.78) SHIP-TREND-0: 1.21 (0.89 to 1.65) MDD lifetime: 1.23 (0.87 to 1.75)	<u>Recurrent MDD</u> Women: 0.73 (0.47 to 1.12) Men: 1.25 (0.81 to 1.93)
Goldbacher et al 2009 <sup>44</sup> (SWAN) (N = 429) Prospective cohort	DSM-IV MDD criteria using SCID-IV	HR (95% CI) depression as a predictor of high fasting glucose; 7-year follow-up <sup>r</sup>	Overall: 1.22 (0.75 to 2.92)	NR
<b>Meta-Analyses</b>				
Cosgrove et al 2008 <sup>27</sup> 14 studies (N = NR)	Any assessment of MDD or raised depression score on a validated scale	Pooled RR (95% CI) risk of developing T2DM associated with depression	<u>Fixed/random effects model</u> Depression score or DIS for diagnosis: <b>1.33 (1.19 to 1.46)/1.17 (1.05 to 1.29)</b> Depression scales for diagnosis: <b>1.42 (1.18 to 1.66)/1.25 (1.02 to 1.48)</b>	NR
Mezuk et al 2008b <sup>45</sup> 20 studies (N = NR)	NR	Pooled RR (95% CI) incident T2DM in people with depression	Overall: <b>1.60 (1.37 to 1.88)</b> Age < 50 years: <b>1.96; P &lt; .001</b> Age ≥ 50 years: <b>1.50; P &lt; .001</b> Women: 1.26 (0.95 to 1.67) Men: <b>1.57 (1.24 to 1.99)</b>	NR
Rotella and Mannucci 2013 <sup>29</sup> 23 studies (N = 424,557)	Any method included	Pooled HR (95% CI) incident diabetes in people with vs without depression	Overall: <b>1.379 (1.227 to 1.550); P &lt; .001</b> Use of antidepressant: <b>1.68 (1.17 to 2.40); P = .005</b> Depression diagnosis, untreated: 1.56 (0.92 to 2.65); P = .09	NR
Vancampfort et al 2015 <sup>30</sup> 17 studies (N = 158,834)	Interview-defined MDD according to the DSM or ICD	Pooled RR (95% CI) risk of T2DM in people with MDD	<b>1.49 (1.29 to 1.72); P &lt; .001</b>	NR

<sup>a</sup>When multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs no depression. Statistically significant differences (P < .05) are shown in bold; P values are reported when available.

<sup>b</sup>For the "Depression Recurrence/Severity" category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>c</sup>Adjusted for age, sex, survey, lifestyle risk factors (smoking, alcohol consumption, physical inactivity), and metabolic risk factors (hypertension, dyslipidemia)

<sup>d</sup>Adjusted for age as a continuous and quadratic variable, sex, and number of physician visits (≥ 5).

<sup>e</sup>Adjusted for age, sex, living situation, educational level, BMI, hypertension, statin use, current smoking, family history, functional disability, alcohol consumption, antidepressant treatment, and antipsychotic treatment.

<sup>f</sup>Adjusted for age, BMI, family history of diabetes, smoking, physical activity, and socioeconomic position. Middle quartiles were combined into a single group

<sup>g</sup>Adjusted for age, sex, and BMI.

<sup>h</sup>Adjusted for age at baseline, sex, race, marital status, education level, BMI, cigarette smoking, functional limitations index, self-report of limited ability to work, and household income.

<sup>i</sup>Study 1: adjusted for sex, hypertension, CHD, cerebrovascular disease, and cancer; Study 2: adjusted for sex. Participants in Study 2 did not have a clear diagnosis of depression, only antidepressant medication use (treatment for > 6 months).

<sup>j</sup>Adjusted for age, marriage status, living alone, hypertension, obesity, smoking, alcohol use, snoring, and sleep difficulty (difficulties initiating sleep; difficulties maintaining sleep) or sleep duration (≤ 5 h and ≥ 9 h).

<sup>k</sup>Significant at a lower level of adjustment only.

<sup>l</sup>Adjusted for age, sex, ethnicity, education, smoking status, alcohol use, antidepressant use, and social network size (1981–2005 analysis); additionally adjusted for BMI, family history of diabetes, stairs climbed per day, frequency of eating balanced meals or social network size, and frequency of social contact with relatives (1993–2005 analysis).

<sup>m</sup>Adjusted for age, sex, and genetic risk.

<sup>n</sup>Adjusted for age, sex, BMI, fasting glucose, SBP, triacylglycerol, HDL cholesterol, smoking, and the presence of the other conditions (CVD, heart failure, chronic kidney disease).

<sup>o</sup>Adjusted for family history of diabetes, marital status, alcohol consumption, smoking status, physical activity level, coffee, whole grain, red/processed meat, and soft drinks.

<sup>p</sup>Adjusted for baseline age, CVD, education, BMI, alcohol use, cigarette use, lifetime anxiety disorder, and stressful events.

<sup>q</sup>Adjusted for age categories, marital status, education, employee status, smoking, physical inactivity, and risky alcohol consumption.

<sup>r</sup>Adjusted for baseline age and race.

Abbreviations: AGE-CAT = Automated Geriatric Examination for Computer Assisted Taxonomy; BMI = body mass index; CES-D = Center for Epidemiologic Studies-Depression; CHD = coronary heart disease; CIDI = Composite International Diagnostic Interview; CIDI-SF = Composite International Diagnostic Interview-Short Form; CID-S = Composite International Diagnostic-Screener; CVD = cardiovascular disease; DEEX = DEpression and EXhaustion subscale; DIS = Diagnostic Interview Schedule; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; ECA = Epidemiologic Catchment Area; GMS = Geriatric Mental State; HDL = high-density lipoprotein; HR = hazard ratio; ICD = *International Classification of Diseases*; KORA = Cooperative Health Research in the Region of Augsburg; M-CIDI = Munich-Composite International Diagnostic Interview; MDD = major depressive disorder; MHI-5 = 5-item Mental Health Inventory; MONICA = Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg; NR = not reported; NS = not significant; OR = odds ratio; RR = risk ratio; SALT = Screening Across the Lifespan Twin; SBP = systolic blood pressure; SCAN = Schedules for the Clinical Assessment of Neuropsychiatry; SCID-IV = Structured Clinical Interview for DSM-IV disorders; SHIP = Study of Health In Pomerania; SWAN = Study of Women's Health Across the Nation; T2DM = type 2 diabetes mellitus; ZARADEMP = Zaragoza Dementia and Depression.

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Supplementary Table 26 for complete details). Findings varied across studies; however, there was a notable trend of a stronger association between depression and incident obesity among women compared with men. In particular, both meta-analyses demonstrated a significant association between depression and incident obesity among all participants and among women-only subgroups but not among men-only subgroups.<sup>47,48</sup> The use of antidepressants has a known association with obesity; the Canadian National Population Health Survey (NPHS) demonstrated that both use of venlafaxine (a serotonin and norepinephrine reuptake inhibitor; HR=4.9; 95% CI, 1.8 to 13.0;  $P<.001$ ) and use of selective serotonin reuptake inhibitors (SSRIs; HR=1.9; 95% CI, 1.2 to 3.2;  $P<.01$ ) were significantly associated with incident obesity, whereas a diagnosis of MDE was not (with or without covariate adjustment for sex, age, overweight body mass index at baseline, level of activity, and antidepressant use).<sup>49</sup> The meta-analyses did not indicate any adjustment for medication use; thus, the potential impact of antidepressants on the findings among men and women subgroups should be taken into account.<sup>47</sup> Of the 10 individual studies identified, only 3 mentioned an adjustment for antidepressant medication; these studies still reported significant associations between depression and obesity in at least some subgroups analyzed (see Supplementary Table 26 for complete details).

### Autoimmune/GI Disorders and Musculoskeletal/Pain Conditions

**Incident autoimmune diseases.** Six studies assessed the impact of depression on the incidence of various autoimmune diseases (see Supplementary Table 27 for complete details). The most comprehensive study was a prospective, population-based analysis of “any” autoimmune disease (including ankylosing spondylitis, autoimmune thyroiditis, celiac disease, Crohn’s disease, idiopathic thrombocytopenic purpura, iridocyclitis, multiple sclerosis, primary adrenocortical insufficiency, psoriasis vulgaris, rheumatoid arthritis, Sjögren’s syndrome, systemic lupus erythematosus, thyrotoxicosis, type 1 diabetes mellitus, and ulcerative colitis) in a series of linked databases assessing a cohort of over 1 million people in Denmark over a 17-year period.<sup>50</sup> In this analysis, a history of depression was significantly associated with the incidence of any autoimmune disease (IRR=1.25; 95% CI, 1.19 to 1.31;  $P<.01$ ).<sup>50</sup> The incidence of certain autoimmune disorders in the same population-based cohort was also shown to be significantly associated with a history of depression, including Crohn’s disease (IRR=1.36; 95% CI, 1.16 to 1.60;  $P<.01$ ), systemic lupus erythematosus (IRR=1.38; 95% CI, 1.00 to 1.91;  $P<0.01$ ), and psoriasis (IRR=1.45; 95% CI, 1.13 to 1.85;  $P<.01$ ).<sup>50</sup> By contrast, a history of depression was not significantly associated with the incidence of ulcerative colitis, celiac disease, or ankylosing spondylitis.<sup>50</sup>

For the multiple sclerosis comorbidity, the Danish population-based cohort demonstrated a significant association between a history of depression and incident

multiple sclerosis (IRR=1.46; 95% CI, 1.26 to 1.69;  $P<.01$ ).<sup>50</sup> In addition, incident multiple sclerosis was significantly associated with a single episode of depression (IRR=1.48; 95% CI, 1.27 to 1.74;  $P<.01$ ) but not multiple episodes of depression (IRR=1.30; 95% CI, 0.88 to 1.92).<sup>50</sup> In alignment with these findings, a study of the Swedish National Patient Register also demonstrated a significant association between depression (overall [HR=1.86; 95% CI, 1.73 to 2.00;  $P<.001$ ] and severe depression [HR=1.46; 95% CI, 1.27 to 1.68;  $P<.0001$ ]) and multiple sclerosis.<sup>51</sup>

The impact of depression on incident rheumatoid arthritis was mixed. The Danish population cohort study reported no significant associations between a history of depression and incident rheumatoid arthritis (IRR=1.01; 95% CI, 0.90 to 1.44),<sup>50</sup> whereas an analysis of The Health Improvement Network (THIN) database found a strong significant association between depression and incident rheumatoid arthritis over a nearly 7-year follow-up (HR=1.38; 95% CI, 1.31 to 1.46;  $P<.0001$ ).<sup>52</sup> A UK-based case-control study showed that, among a group of people with recurrent depression, there were elevated odds of rheumatoid arthritis (OR=2.72; 95% CI, 1.31 to 5.63).<sup>35</sup> However, when corrected for multiple testing, this association was not considered to be significant ( $P=.10$ ). The Canadian NPHS study reported that MDD at baseline led to a significant association with arthritis/rheumatism over the 8-year follow-up (HR=1.7; 95% CI, 1.3 to 2.2); when assessed based on duration of past-year depressive episodes, this was significant only for those with a depression episode of 13–52+ weeks (HR=2.2; 95% CI, 1.5 to 3.3) and not for those with a duration of 2–12 weeks (HR=1.2; 95% CI, 0.8 to 1.7).<sup>19</sup>

**Incident headache and other chronic pain.** Four studies (5 publications) described the association between depression and migraine or headache; most (3 of 4) did not show a significant association in the fully adjusted models for baseline depression and risk of “any” migraine, although some significant associations were reported between depression presence/severity and migraine with aura (see Supplementary Table 28 for complete details). Three studies that assessed other pain-related outcomes (spinal pain, temporomandibular pain, and back problems) generally did not show an association between depression presence or severity and incident pain, with the exception of back problems reported in 1 study (see Supplementary Table 28 for complete details).<sup>19</sup> In parallel with the single-study finding, a meta-analysis of 11 studies assessing the association between depression and low-back pain reported a pooled OR of 1.59 (95% CI, 1.26 to 2.01), demonstrating a significant association, and this relationship remained significant across all subgroup and sensitivity analyses (method of depression diagnosis, whether studies adjusted for confounders, and studies restricted to older participants).<sup>53</sup> The meta-analysis also showed that this association was affected by depression severity, with a significant association observed for people with the most-severe level of depression (OR=2.51; 95% CI, 1.58 to 3.99)

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 but not for the lowest level of depression severity (OR = 1.51; 95% CI, 0.89 to 2.56).<sup>53</sup>

### Infectious Diseases

Searches for infectious diseases identified 3 studies assessing the relationship between MDD and HIV infection. A US-based Medicaid-eligible cohort analysis of over 4 million people demonstrated that baseline MDD was associated with increased odds of incident HIV/AIDS in people both with (OR = 3.04; 95% CI, 2.75 to 3.36;  $P < .001$ ) and without (OR = 1.12; 95% CI, 1.04 to 1.21;  $P < .01$ ) concurrent substance abuse disorder.<sup>54</sup> Furthermore, among HIV-infected individuals, the odds of low HIV RNA levels (ie, maintaining viral suppression) at 12 months were significantly decreased in those with depression who did not use SSRIs compared with those who did not have depression (OR = 0.77; 95% CI, 0.62 to 0.95;  $P = .02$ ).<sup>55</sup> Similar findings were observed in a study that used generalized linear mixed models to show that individuals classified as having “moderate-increasing” depression severity led to significantly greater odds of a low CD4 count (ie, disease worsening) compared with “low-chronic” depression (OR = 1.53; 95% CI, 1.08 to 2.19).<sup>56</sup>

### Respiratory Disorders

The review identified 3 studies assessing the relationship between MDD and respiratory disorders, including asthma and bronchitis. Although several significant associations were identified, directionality was often unclear. For example, in a case-control analysis based in the United Kingdom, people with recurrent depression reported significantly higher lifetime asthma (OR = 2.19; 95% CI, 1.53 to 3.13;  $P = .00022$ ), but the methods did not permit clear confirmation of whether depression preceded asthma.<sup>35</sup> Similarly, an analysis from the cross-sectional National Health and Nutrition Examination Survey (NHANES) study demonstrated a significantly increased prevalence of asthma according to both presence and severity of depression (OR = 3.18; 95% CI, 2.37 to 4.26;  $P < .01$  for moderately severe; OR = 3.95; 95% CI, 2.38 to 6.56;  $P < .01$  for severe depression).<sup>57</sup> However, the directionality was again unclear because the cross-sectional study design did not account for the order in which these disorders occurred in participants.<sup>57</sup> The Canadian NPHS study showed significant associations with incident asthma and bronchitis in both people who had MDD at baseline (HR = 1.8; 95% CI, 1.3 to 2.5 for asthma; HR = 2.1; 95% CI, 1.5 to 2.9 for bronchitis) and those who had MDD assessed as a time-varying characteristic (HR = 1.7; 95% CI, 1.2 to 2.4 for asthma; HR = 2.6; 95% CI, 1.9 to 3.7 for bronchitis) throughout the 8-year follow-up, regardless of duration of depression and covariates added to the model.<sup>19</sup>

### Substance Abuse

A total of 23 observational study publications that described the association between depression and substance abuse were identified by the review, including multiple

analyses from several large studies such as the Canadian NPHS cohort, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) cohort, and the cross-sectional annual National Survey on Drug Use and Health (NSDUH) survey in the United States. Results varied widely among studies that assessed the impact of depression on incident alcohol or cannabis abuse or related disorders. In general, a greater proportion of studies did not show a significant association with incident drug or alcohol abuse, although there appeared to be a consistent relationship between MDD severity and these incidences (see Supplementary Table 30 for complete information). Furthermore, studies showed a consistent impact of depression on the severity of alcohol abuse, particularly among the young adult cohorts (see Supplementary Table 31 for complete information).

### Quality Assessment

Quality assessment was conducted for 198 of the 199 included studies; 1 study did not undergo quality assessment because it lacked a validated checklist. Most studies were assessed to be truly or somewhat representative of the average population in the community and selected their comparator group (cohort, controls) using sufficient methods from either the same population or the general community. In addition, most studies were deemed to adequately control for the most important factors and often for additional important factors; this was likely a reflection of the covariate adjustment required by the review inclusion criteria. However, several cohort studies lost >20% of participants to follow-up or provided insufficient information about follow-up rates; approximately half of the case-control studies provided no description of the nonresponse rate (ie, dropouts) among both groups; and all cross-sectional studies either did not describe their statistical test or used one that was incomplete or not appropriate. Further details of the quality assessment for individual studies are reported in Supplementary Tables 4–7.

### DISCUSSION

In a systematic review of nearly 200 studies, the presence of MDD was identified as a risk factor for both the development and the worsening of a range of comorbidities in several categories, including CNS disorders (eg, dementia/Alzheimer’s disease and Parkinson’s disease), CVD (eg, general CVD, ischemic heart/coronary artery disease, MI, and heart failure), metabolic and endocrine disorders (particularly diabetes in men and obesity in women), certain autoimmune disorders (such as Crohn’s disease, psoriasis, and multiple sclerosis), and substance use disorders. These associations were observed consistently despite the notable variability in methodology across studies, including population sampled, criteria for depression, length of follow-up, and covariates included in the analysis. Although the association was less consistent between

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depression and other comorbidity categories, significant associations were often observed for certain subgroups or specific relationships. For other associations, such as those in the cancer category, wide confidence intervals were often observed, which was likely influenced to some extent by the heterogeneity of these comorbid diseases. It should also be noted that within multiple studies, certain associations strengthened with increasing depression severity or with increasing number of depressive episodes.

The effects of depression on comorbidities can arise both directly, through biological pathways, and indirectly, through a reduced ability to care for oneself or other risky health behaviors. Several biological mechanisms have been implicated in the potential relationship between depression and physical comorbidities; many of these involve dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis and its impact on cortisol levels and the immune system. In particular, it has been suggested that elevated cortisol is responsible for activating cancer cell growth pathways *in vitro*<sup>58</sup> and for hippocampal atrophy, accumulation of amyloid- $\beta$  plaques, inflammatory processes, blood flow alterations, and lack of nerve growth factors in people with dementia and Alzheimer's disease.<sup>59,60</sup> Inflammation, whether activated by HPA axis dysfunction or other mechanisms such as the sympathetic nervous system, has been suggested as a contributing factor to the biological mechanisms underpinning depression, and the association between depression and several inflammation-related disorders (such as Crohn's disease and coronary heart disease) could be thus explained to some degree by inflammation.<sup>61</sup> Elevated cortisol may also be responsible for visceral fat accumulation, insulin resistance (type 2 diabetes), and disturbances in lipid metabolism in people with metabolic and endocrine disorders.<sup>62,63</sup> It also remains possible, however, that depression could be a prodromal symptom of certain neurologic disorders, which was acknowledged by authors of included studies that identified associations between depression and dementia,<sup>64</sup> Parkinson's disease,<sup>65,66</sup> and stroke.<sup>67</sup> However, in a sensitivity analysis of the Pathways Epidemiologic Study that excluded people with an *International Classification of Diseases, 9th revision (ICD-9)* diagnosis of dementia in the 2 years after baseline, depression remained associated with an increased risk of dementia, suggesting that depression was less likely to be a prodromal symptom or secondary to dementia.<sup>68</sup> Depression could be both a causal factor and a prodromal symptom for these neurologic disorders, and additional research could further clarify the directionality of this relationship.

In addition to biological mechanisms, depression may impact a person's ability to take care of themselves, seek care, and adhere to treatment recommendations, which could lead to an increased risk of developing comorbidities and/or a worsened disease course. For example, many studies acknowledged the role that diet and lifestyle factors could play, in addition to biological mechanisms, for the association between depression and CVD.<sup>69-72</sup> In

addition, many substance abuse studies focused on the self-medication hypothesis as a primary factor that was likely to be mediating the association between depression and substance abuse.<sup>73</sup>

The relationship between physical and mental health has several implications for the integration of care and the need for further education among physicians, patients, caregivers, and society. Certain clinical guidelines as well as various government and patient organizations have begun to address comorbidities among people with MDD to varying degrees. For example, both the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 guidelines and the US Centers for Disease Control and Prevention (CDC) note that depression is an independent risk factor for several diseases.<sup>74,75</sup> The CDC recommends actively addressing mental health disorders early along with providing support to improve healthy behaviors as a strategy to decrease the risk of physical comorbidities such as cardiovascular events<sup>76</sup>; suggested actions to promote heart disease prevention include integrating mental health into multidisciplinary teams and incorporating mental health screening in the care of other diseases. However, there remains considerable room to further acknowledge and explore the relationship between depression and comorbidities and to update guidelines and other educational tools to incorporate recommendations that are informed by the link between mental and physical health.

Several limitations should be acknowledged when interpreting the results of this review. First, the observational study search and screen were date-limited to studies published between the years 2005 and 2020, and therefore any relevant studies outside of this range were not included in the evidence summary. In addition, based on their design, some studies may not present a true causal relationship in which depression occurred before the comorbidity in all individuals. It should also be noted that some of these findings could be explained to a degree by changes in patient care following a depression diagnosis and not an actual causal relationship between depression and a comorbidity. For example, if a person is diagnosed with depression, he or she may undergo more frequent contact with health care providers, which could in turn lead to the identification of diseases that had previously gone undiagnosed.

In conclusion, the presence of MDD was identified as a statistically significant risk factor for both the development and the worsening of a range of comorbidities. Collectively, these results highlight that depression may impact many comorbidities concurrently and could thus have a considerable negative impact on a person's whole health. Additional research assessing the combined comorbidity risks may be warranted to further our understanding of the collective burden of depression-associated comorbidities. Furthermore, addressing depression with appropriate services, treatment, and support could have a broad positive impact on physical health, thus renewing the importance of appropriately timed screening and diagnosis of depression and adequate treatment of MDD.

**Submitted:** November 18, 2021; accepted June 27, 2022.

**Published online:** October 19, 2022.

**Relevant financial relationships:** Mr Suthoff is a current employee and Ms Arnaud and Dr Werneburg are former employees of Sage Therapeutics, Inc., and own stock/stock options. Drs Reinhart and Aleksanderek are current or former employees of Tantalus Medical Communications, Ltd, which received financial support from Sage Therapeutics, Inc., and Biogen, Inc., for research and medical writing support. During the peer review process, both Sage Therapeutics, Inc., and their collaboration partner Biogen, Inc., had the opportunity to review and comment on this manuscript; however, the authors had full editorial control of the manuscript and provided final approval on all content. Ms Fulwider has received consulting fees from Sage Therapeutics, Inc. Drs Brister and Duckworth and Ms Foxworth have nothing to disclose.

**Funding/support:** This work was supported by Sage Therapeutics, Inc., and Biogen, Inc.

**Role of the sponsor:** Employees of Sage Therapeutics, Inc., contributed to the protocol design and manuscript drafting and review but had no role in the screening and study selection for inclusion in the systematic review.

**Previous presentation:** Portions of this work were previously presented as an abstract at the International Society for Pharmacoeconomics and Outcomes Research Annual Meeting; May 18–20, 2020 (virtual meeting).

**Acknowledgments:** The authors thank Katie Stenson, MSc, a former employee of Sage Therapeutics, Inc., for contributions to the design and interpretation of the systematic review and Shawn Eapen, MSc, and Sara Watchko, MPH, both affiliates of Tantalus Medical Communications (Victoria, BC, Canada) for assistance with the systematic review. Mr Eapen and Ms Watchko have no conflicts of interest to declare. The authors thank Tantalus Medical Communications for providing research and medical writing support, which was funded by Sage Therapeutics, Inc., and Biogen, Inc., in accordance with Good Publication Practice (GPP3) guidelines.

**Supplementary material:** Available at Psychiatrist.com.

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## **Supplementary Material**

**Article Title:** Impact of Major Depressive Disorder on Comorbidities: A Systematic Literature Review

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**DOI Number:** <https://doi.org/10.4088/JCP.21r14328>

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15. [Table 15](#) Summary of studies assessing the association between depression and heart failure severity or mortality
16. [Table 16](#) Summary of studies assessing the association between depression and hypertension incidence
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29. [Table 29](#) Summary of studies assessing the association between depression and pain severity
30. [Table 30](#) Summary of studies assessing the association between depression and substance use disorder incidence
31. [Table 31](#) Summary of studies assessing the association between depression and substance use disorder severity

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## Search strategy

Supplementary Table 1. Database search strategy

Auto-immune/infectious	Cancer	CNS	CVD	GI	Metabolic/endocrine	Musculo-skeletal/pain	Respiratory	Substance abuse
# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search
<b>Embase</b>								
1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.	1 exp major depression/ (major adj2 depress*).ab, ti.
2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.
3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2
4 case control study/	4 case control study/	4 case control study/	4 case control study/	4 case control study/	4 case control study/	4 case control study/	4 case control study/	4 case control study/
5 cohort analysis/	5 cohort analysis/	5 cohort analysis/	5 cohort analysis/	5 cohort analysis/	5 cohort analysis/	5 cohort analysis/	5 cohort analysis/	5 cohort analysis/
6 longitudinal study/	6 longitudinal study/	6 longitudinal study/	6 longitudinal study/	6 longitudinal study/	6 longitudinal study/	6 longitudinal study/	6 longitudinal study/	6 longitudinal study/
7 prospective study/	7 prospective study/	7 prospective study/	7 prospective study/	7 prospective study/	7 prospective study/	7 prospective study/	7 prospective study/	7 prospective study/
8 retrospective study/	8 retrospective study/	8 retrospective study/	8 retrospective study/	8 retrospective study/	8 retrospective study/	8 retrospective study/	8 retrospective study/	8 retrospective study/
9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.	9 (case control adj (study or studies)).tw.
10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.	10 (cohort adj (study or studies)).tw.
11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.	11 (cross sectional adj (study or studies)).tw.
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13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.	13 (observational adj (study or studies)).tw.
14 or/4-13	14 or/4-13	14 or/4-13	14 or/4-13	14 or/4-13	14 or/4-13	14 or/4-13	14 or/4-13	14 or/4-13



<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>
15 randomized controlled trial/	15 randomized controlled trial/	15 randomized controlled trial/	15 randomized controlled trial/	15 randomized controlled trial/	15 randomized controlled trial/	15 randomized controlled trial/	15 randomized controlled trial/	15 randomized controlled trial/
16 14 not 15	16 14 not 15	16 14 not 15	16 14 not 15	16 14 not 15	16 14 not 15	16 14 not 15	16 14 not 15	16 14 not 15
17 exp acquired immune deficiency syndrome/	17 exp malignant neoplasm/	17 exp dementia/	17 exp ischemic heart disease/	17 exp gastrointestinal disease/	17 exp metabolic syndrome X/	17 exp arthritis/	17 exp asthma/	17 exp substance abuse/
18 exp Human immunodeficiency virus/	18 cancer.ab,ti.	18 exp Alzheimer disease/	18 exp cardiovascular disease/	18 exp esophagitis/	18 exp diabetes mellitus/	18 exp rheumatoid arthritis/	18 exp chronic lung disease/	18 exp drug abuse/
19 exp ankylosing spondylitis/	19 17 or 18	19 exp epilepsy/	19 exp hypertension/	19 exp gastrointestinal hemorrhage/	19 exp hyperlipidemia/	19 exp backache/	19 exp bronchitis/	19 exp alcohol abuse/
20 exp autoimmune disease/	20 3 and 16 and 19	20 exp Parkinson disease/	20 exp coronary artery disease/	20 exp Escherichia coli infection/	20 exp lupus vulgaris/	20 exp chronic pain/	20 exp chronic obstructive lung disease/	20 ((substance or drug or alcohol) adj2 abus*).ab,ti.
21 exp celiac disease/	21 (review not systematic review).pt.	21 (dementia or Alzheimer* or epilepsy or Parkinson*).ab,ti.	21 exp heart infarction/	21 exp gastroesophageal reflux/	21 exp systemic lupus erythematosus/	21 exp fibromyalgia/	21 exp emphysema/	21 or/17-20
22 exp Crohn disease/	22 20 and 21	22 or/17-21	22 exp cerebrovascular accident/	22 exp irritable colon/	22 exp obesity/	22 exp headache/	22 (asthma or (chronic adj2 (pulmonary or lung) adj (disease or disorder)) or COPD or bronchitis or emphysema).ab,ti.	22 3 and 16 and 21
23 exp multiple sclerosis/	23 20 not 22	23 3 and 16 and 22	23 ((coronary adj (artery or heart) adj (disease) or cardiovascular disease or CVD or hypertension or ischemic heart disease or MI or	23 ((gastrointestinal adj (disease or h?emorrhage)) or esophagitis or Escherichia coli infection or "e.coli infection" or	23 exp ovary polycystic disease/	23 exp migraine/	23 or/17-22	23 (review not systematic review).pt.

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
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			myocardial infarction or stroke or cerebrovascular accident or CVA).ab,ti.	(gastroesophageal reflux disease*) or GERD or (irritable bowel disease or syndrome) or IBS).ab,ti.				
24 exp psoriasis vulgaris/	24 limit 23 to (editorial or letter or note)	24 (review not systematic review).pt.	24 or/17-23	24 or/17-23	24 (metabolic syndrome or diabet* or hyperlipid?emi* or lupus or obes* or polycystic ovar* syndrome or ovar* polycystic disease or PCOS).ab,ti.	24 exp osteoporosis/	24 3 and 16 and 23	24 22 and 23
25 exp ulcerative colitis/	25 23 not 24	25 23 and 24	25 3 and 16 and 24	25 3 and 16 and 24	25 or/17-24	25 (arthriti* or backache or (chronic adj pain) or fibromyalgia or headache or migraine or ((back or head) adj2 (ache or pain)) or joint disorder or osteoporosis).ab,ti.	25 (review not systematic review).pt.	25 22 not 24
26 (AIDS or acquired immune deficiency syndrome or HIV or human immunodeficiency virus or	26 limit 25 to (conference abstract or conference paper or "conference review")	26 23 not 25	26 (review not systematic review).pt.	26 (review not systematic review).pt.	26 3 and 16 and 25	26 or/17-25	26 24 and 25	26 limit 25 to (editorial or letter or note)

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>
ankylosing spondylitis or (autoimmune adj (disorder or disease)) or c?eliac or crohn* or MS or multiple sclerosis or psoriasis or ulcerative colitis).ab,ti.								
27 or/17-26	27 25 not 26	27 limit 26 to (editorial or letter or note)	27 25 and 26	27 25 and 26	27 (review not systematic review).pt.	27 3 and 16 and 26	27 24 not 26	27 25 not 26
28 3 and 16 and 27	28 limit 27 to english language	28 26 not 27	28 25 not 27	28 25 not 27	28 26 and 27	28 (review not systematic review).pt.	28 limit 27 to (editorial or letter or note)	28 limit 27 to (conference abstract or conference paper or "conference review")
29 (review not systematic review).pt.		29 limit 28 to (conference abstract or conference paper or "conference review")	29 limit 28 to (editorial or letter or note)	29 limit 28 to (editorial or letter or note)	29 26 not 28	29 27 and 28	29 27 not 28	29 27 not 28
30 28 and 29		30 28 not 29	30 28 not 29	30 28 not 29	30 limit 29 to (editorial or letter or note)	30 27 not 29	30 limit 29 to (conference abstract or conference paper or "conference review")	30 limit 29 to english language
31 28 not 30		31 limit 30 to english language	31 limit 30 to (conference abstract or conference paper or "conference review")	31 limit 30 to (conference abstract or conference paper or "conference review")	31 29 not 30	31 limit 30 to (editorial or letter or note)	31 29 not 30	

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
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32 limit 31 to (editorial or letter or note)			32 30 not 31	32 30 not 31	32 limit 31 to (conference abstract or conference paper or "conference review")	32 30 not 31	32 limit 31 to english language	
33 31 not 32			33 limit 32 to english language	33 limit 32 to english language	33 31 not 32	33 limit 32 to (conference abstract or conference paper or "conference review")		
34 limit 33 to (conference abstract or conference paper or "conference review")					34 limit 33 to english language	34 32 not 33		
35 33 not 34						35 limit 34 to english language		
36 limit 35 to english language								

**MEDLINE**

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4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/	4 exp Case Control Studies/
5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/	5 exp Cohort Studies/
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<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
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9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.	9 (follow up adj (study or studies)).tw.
10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.	10 (observational adj (study or studies)).tw.
11 longitudinal.tw.	11 longitudinal.tw.	11 longitudinal.tw.	11 longitudinal.tw.	11 longitudinal.tw.	11 longitudinal.tw.	11 longitudinal.tw.	11 longitudinal.tw.	11 longitudinal.tw.
12 retrospective.tw.	12 retrospective.tw.	12 retrospective.tw.	12 retrospective.tw.	12 retrospective.tw.	12 retrospective.tw.	12 retrospective.tw.	12 retrospective.tw.	12 retrospective.tw.
13 cross sectional.tw.	13 cross sectional.tw.	13 cross sectional.tw.	13 cross sectional.tw.	13 cross sectional.tw.	13 cross sectional.tw.	13 cross sectional.tw.	13 cross sectional.tw.	13 cross sectional.tw.
14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14	14 Cross-Sectional Studies/or/4-14
15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16	15 Randomized Controlled Trial/15 not 16
16 exp Acquired Immunodeficiency Syndrome/exp HIV/	16 exp Neoplasms/cancer.ab.ti.	16 exp Dementia/Alzheimer Disease/	16 exp Myocardial Ischemia/	16 exp Gastrointestinal Diseases/	16 exp Metabolic Syndrome/	16 exp Arthritis/	16 exp Asthma/	16 exp Substance-Related Disorders/
17 exp Spondylitis, Ankylosing/	17 18 or 19	17 exp Epilepsy/	17 exp Cardiovascular Diseases/	17 exp Hypertension/	17 exp Hyperlipidemias/	17 exp Arthritis, Rheumatoid/	17 exp Lung Diseases/	17 exp Alcoholism/
18 exp Autoimmune Diseases/	18 3 and 17 and 20	18 exp Parkinson Disease/	18 exp Coronary Artery Disease/	18 exp Escherichia coli Infections/	18 exp Lupus Vulgaris/	18 exp Chronic Pain/	18 exp Pulmonary Disease, Chronic Obstructive/	18 ((substance or drug or alcohol) adj2 abus*).ab.ti.

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>
22 exp Celiac Disease/	22 (review not systematic review).pt.	22 (dementia or Alzheimer* or epilepsy or Parkinson*).ab,ti.	22 exp Myocardial Infarction/	22 exp Gastroesophageal Reflux/	22 exp Lupus Erythematosus, Systemic/	22 exp Fibromyalgia/	22 exp Emphysema/	22 3 and 17 and 21
23 exp Crohn Disease/	23 21 and 22	23 or/18-22	23 exp Stroke/	23 exp Irritable Bowel Syndrome/	23 exp Obesity/	23 exp Headache/	23 (asthma or ((pulmonary or lung) adj (disease or disorder)) or chronic obstructive pulmonary disease or COPD or bronchitis or emphysema).ab,ti.	23 (review not systematic review).pt.
24 exp Multiple Sclerosis/	24 21 not 23	24 3 and 17 and 23	24 (MI or myocardial ischemi* or cardiovascular disease or CVD or hypertension or (coronary adj (artery or heart) adj disease) or coronary disease or myocardial infarct* or stroke).ab,ti.	24 ((gastrointestinal adj (disease or hemorrhage)) or esophagitis or Escherichia coli infection or "e.coli infection" or (gastroesophageal adj reflux adj disease*) or GERD or (irritable bowel adj (disease or syndrome)) or IBS).ab,ti.	24 exp Polycystic Ovary Syndrome/	24 exp Migraine Disorders/	24 or/18-23	24 22 and 23
25 exp Psoriasis/	25 limit 24 to (case reports or comment or editorial or letter)	25 (review not systematic review).pt.	25 or/18-24	25 or/18-24	25 (metabolic syndrome or diabet* or hyperlipid?emi* or lupus	25 exp Osteoporosis/	25 3 and 17 and 24	25 22 not 24

<b>Auto-immune/ infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/ endocrine</b>	<b>Musculo- skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>
26 exp Colitis, Ulcerative/	26 24 not 25	26 24 and 25	26 3 and 17 and 25	26 3 and 17 and 25	26 or/18-25 or obes* or polycystic ovar* syndrome or PCOS).ab,ti.	26 (arthriti* or (chronic adj pain) or fibromyalgia or headache or migraine or ((back or head) adj2 (ache or pain)) or joint disorder or osteoporosis).ab,ti.	26 (review not systematic review).pt.	26 limit 25 to (case reports or comment or editorial or letter)
27 (AIDS or acquired immune deficiency syndrome or HIV or human immunodeficiency virus or ankylosing spondylitis or (autoimmune adj (disorder or disease)) or c?eliac or crohn* or MS or multiple sclerosis or psoriasis or ulcerative colitis).ab,ti.	27 limit 26 to english language	27 24 not 26	27 (review not systematic review).pt.	27 (review not systematic review).pt.	27 3 and 17 and 26	27 or/18-26	27 25 and 26	27 25 not 26
28 or/18-27		28 limit 27 to (case reports or comment or editorial or letter)	28 26 and 27	28 26 and 27	28 (review not systematic review).pt.	28 3 and 17 and 27	28 25 not 27	28 limit 27 to english language

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>
29 3 and 17 and 28		29 27 not 28	29 26 not 28	29 26 not 28	29 27 and 28	29 (review not systematic review).pt.	29 limit 28 to (case reports or comment or editorial or letter)	
30 (review not systematic review).pt.		30 limit 29 to english language	30 limit 29 to (case reports or comment or editorial or letter)	30 limit 29 to (case reports or comment or editorial or letter)	30 27 not 29	30 28 and 29	30 28 not 29	
31 29 and 30			31 29 not 30	31 29 not 30	31 limit 30 to (case reports or comment or editorial or letter)	31 28 not 30	31 limit 30 to english language	
32 29 not 31			32 limit 31 to english language	32 limit 31 to english language	32 30 not 31	32 limit 31 to (case reports or comment or editorial or letter)		
33 limit 32 to (case reports or comment or editorial or letter)					33 limit 32 to english language	33 31 not 32		
34 32 not 33						34 limit 33 to english language		
35 limit 34 to english language								
<b>PsycINFO</b>								
1 exp Major Depression/	1 exp Major Depression/	1 exp Major Depression/	1 exp Major Depression/	1 exp Major Depression/	1 exp Major Depression/	1 exp Major Depression/	1 exp Major Depression/	1 exp Major Depression/
2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.	2 (major adj2 depress*).ab, ti.
3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2	3 1 or 2
4 c ase control.tw.	4 case control.tw.	4 case control.tw.	4 case control.tw.	4 case control.tw.	4 case control.tw.	4 case control.tw.	4 case control.tw.	4 case control.tw.
5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.	5 (cohort adj (study or studies)).tw.



<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>	<b># Search</b>
6 cohort analy\$.tw.	6 cohort analy\$.tw.	6 cohort analy\$.tw.	6 cohort analy\$.tw.	6 cohort analy\$.tw.	6 cohort analy\$.tw.	6 cohort analy\$.tw.	6 cohort analy\$.tw.	6 cohort analy\$.tw.
7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.	7 (follow up adj (study or studies)).tw.
8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.	8 (observational adj (study or studies)).tw.
9 longitudinal.tw.	9 longitudinal.tw.	9 longitudinal.tw.	9 longitudinal.tw.	9 longitudinal.tw.	9 longitudinal.tw.	9 longitudinal.tw.	9 longitudinal.tw.	9 longitudinal.tw.
10 retrospective.tw.	10 retrospective.tw.	10 retrospective.tw.	10 retrospective.tw.	10 retrospective.tw.	10 retrospective.tw.	10 retrospective.tw.	10 retrospective.tw.	10 retrospective.tw.
11 cross sectional.tw.	11 cross sectional.tw.	11 cross sectional.tw.	11 cross sectional.tw.	11 cross sectional.tw.	11 cross sectional.tw.	11 cross sectional.tw.	11 cross sectional.tw.	11 cross sectional.tw.
12 or/4-11	12 or/4-11	12 or/4-11	12 or/4-11	12 or/4-11	12 or/4-11	12 or/4-11	12 or/4-11	12 or/4-11
13 Randomized Controlled Trials/	13 Randomized Controlled Trials/	13 Randomized Controlled Trials/	13 Randomized Controlled Trials/	13 Randomized Controlled Trials/	13 Randomized Controlled Trials/	13 Randomized Controlled Trials/	13 Randomized Controlled Trials/	13 Randomized Controlled Trials/
14 12 not 13	14 12 not 13	14 12 not 13	14 12 not 13	14 12 not 13	14 12 not 13	14 12 not 13	14 12 not 13	14 12 not 13
15 exp AIDS/	15 exp Neoplasms/	15 exp Dementia/	15 exp Heart Disorders/	15 exp Gastrointestinal Disorders/	15 exp Metabolic Syndrome/	15 exp Arthritis/	15 exp Asthma/	15 exp Drug Abuse/
16 exp HIV/	16 cancer.ab.ti.	16 exp Alzheimer's Disease/	16 exp Cardiovascular Disorders/	16 exp Irritable Bowel Syndrome/	16 exp Diabetes Mellitus/	16 exp Rheumatoid Arthritis/	16 exp Lung Disorders/	16 exp Alcohol Abuse/
17 exp immunologic disorders/	17 15 or 16	17 exp Epilepsy/	17 exp Hypertension/	17 ((gastrointestinal adj (disease or hemorrhage)) or esophagitis or Escherichia coli infection or "e.coli infection" or (gastroesophageal adj reflux adj disease*) or GERD or (irritable bowel adj	17 exp Lupus/	17 exp Back Pain/	17 exp Bronchial Disorders/	17 ((substance or drug or alcohol) adj2 abus*).ab.ti.

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search
18 exp Celiac Disease/	18 3 and 14 and 17	18 exp Parkinson's Disease/	18 exp Myocardial Infarctions/	18 or/15-17 (disease or syndrome) or IBS).ab.ti.	18 exp Obesity/	18 exp Chronic Pain/	18 exp Chronic Obstructive Pulmonary Disease/	18 or/15-17
19 exp Multiple Sclerosis/	19 limit 18 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)	19 (dementia or Alzheimer* or epilepsy or Parkinson*).ab.ti.	19 exp Cerebrovascular Accidents/	19 3 and 14 and 18	19 (metabolic syndrome or diabet* or hyperlipid?emi* or lupus or obes* or polycystic ovar* syndrome or ovar* polycystic disease or PCOS).ab.ti.	19 exp Fibromyalgia/	19 exp Pulmonary Emphysema/	19 3 and 14 and 18
20 exp Ulcerative Colitis/	20 18 not 19	20 or/15-19	20 ((coronary adj (artery or heart) adj disease) or (cardiovascular adj (disease or disorder)) or CVD or hypertension or ischemic heart disease or MI or myocardial infarction or stroke or cerebrovascular accident or CVA).ab.ti.	20 limit 19 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)	20 or/15-19	20 exp Headache/	20 (asthma or (chronic adj2 (pulmonary or lung) adj (disease or disorder)) or COPD or bronchitis or emphysema).ab.ti.	20 limit 19 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)
21 (AIDS or acquired immune deficiency syndrome or HIV or human	21 limit 20 to english language	21 3 and 14 and 20	21 or/15-20	21 19 not 20	21 3 and 14 and 20	21 exp Migraine Headache/	21 or/15-20	21 19 not 20

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>
# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search
immunodeficiency virus or ankylosing spondylitis or (autoimmune adj (disorder or disease)) or c?eliac or crohn* or MS or multiple sclerosis or psoriasis or ulcerative colitis).ab,ti. 22 or/15-21		22 limit 21 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)	22 3 and 14 and 21	22 limit 21 to english language	22 limit 21 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)	22 exp Osteoporosis/	22 3 and 14 and 21	22 limit 21 to english language
23 3 and 14 and 22		23 21 not 22	23 limit 22 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)		23 21 not 22	23 (arthriti* or backache or (chronic adj pain) or fibromyalgia or headache or migraine or ((back or head) adj2 (ache or pain)) or joint disorder or osteoporosis).ab,ti.	23 limit 22 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)	
24 limit 23 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)		24 limit 23 to english language	24 22 not 23		24 limit 23 to english language	24 or/15-23	24 22 not 23	

<b>Auto-immune/infectious</b>	<b>Cancer</b>	<b>CNS</b>	<b>CVD</b>	<b>GI</b>	<b>Metabolic/endocrine</b>	<b>Musculo-skeletal/pain</b>	<b>Respiratory</b>	<b>Substance abuse</b>	
# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search	# Search	
25	23 not 24		25	limit 24 to english language		25	3 and 14 and 24	25	limit 24 to english language
26	limit 25 to english language					26	limit 25 to ("column/opinion" or "comment/reply" or editorial or letter or reviews)		
						27	25 not 26		
						28	limit 27 to english language		

**Cochrane Database of Systematic Reviews**

1	(major adj2 depress*).ab, ti.	1	(major adj2 depress*).ab, ti.	1	(major adj2 depress*).ab, ti.	1	(major adj2 depress*).ab, ti.	1	(major adj2 depress*).ab, ti.	1	(major adj2 depress*).ab, ti.	1	(major adj2 depress*).ab, ti.				
2	(AIDS or acquired immune deficiency syndrome or HIV or human immunodeficiency virus or ankylosing spondylitis or (autoimmune adj (disorder or disease)) or c?eliac or crohn* or MS or multiple sclerosis or psoriasis or ulcerative colitis).ab,ti.	2	(cancer or malignant neoplasm).ab, ti.	2	(dementia or Alzheimer* or epilepsy or Parkinson*).ab,ti.	2	((((coronary adj (artery or heart) adj (disease or cardiovascular disease or CVD or hypertension or ischemic heart disease or MI or (myocardial or heart) adj infarction) or stroke or cerebrovascular accident or CVA).ab,ti.	2	((gastrointestinal adj (disease or h?emorrhage)) or esophagitis or Escherichia coli infection or "e.coli infection" or (gastroesophageal adj reflux adj disease*) or GERD or (irritable bowel adj (disease or syndrome)) or IBS).ab,ti.	2	((metabolic syndrome or diabet* or hyperlipidemi* or lupus or obes* or polycystic ovar* syndrome or ovar* polycystic disease or PCOS).ab,ti.	2	(arthriti* or backache or (chronic adj pain) or fibromyalgia or headache or migraine or ((back or head) adj2 (ache or pain)) or joint disorder or osteoporosis).ab,ti.	2	((asthma or (chronic adj2 (pulmonary or lung) adj (disease or disorder)) or COPD or bronchitis or emphysema).ab,ti.	2	((substance or drug or alcohol) adj2 abus*).ab,ti.
3	1 and 2	3	1 and 2	3	1 and 2	3	1 and 2	3	1 and 2	3	1 and 2	3	1 and 2				

## List of congresses searched

- Academy of Managed Care Pharmacy (AMCP) – Annual Meeting and Nexus
- American Psychological Association (APA)
- European Psychological Association (EPA)
- European College of Neuropsychopharmacology (ECNP)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) – all conferences

## Screening criteria

**Supplementary Table 2. Study inclusion and exclusion criteria**

	<b>Inclusion criteria</b>	<b>Exclusion criteria</b>
<b>Population</b>	Diagnosis of MDD <sup>a</sup> Adults ≥18 years of age	Mixed population where MDD subgroup is not reported separately Age <18 years
<b>Intervention(s)</b>	Any or none	No restrictions
<b>Comparator(s)</b>	Any or none	No restrictions
<b>Outcomes</b>	Impact of MDD (including prevalence <sup>b</sup> or change in disease severity <sup>c</sup> ) on the risk of developing comorbidities Impact of MDD (including prevalence <sup>a</sup> or disease severity <sup>b</sup> ) on the change in severity preexisting comorbidities	No outcomes of interest
<b>Study type</b>	Observational studies (i.e. case-control, cohort, cross-sectional) SLRs of observational studies with meta-analysis	Non-human studies Case series, case report Commentaries and letters Recommendations/guidelines Methods articles/protocols Hypothetical models Narrative reviews
<b>Other</b>	English language only Located in Europe and North America	Non-English language Local studies in countries outside of Europe and North America

<sup>a</sup> MDD could include a formal physician diagnosis or any other author-defined criteria for depression that was not clearly non-MDD (such as dysthymia).

<sup>b</sup> “Prevalence” includes studies that compare the risk of comorbidities developing or worsening in an MDD versus non-MDD cohort.

<sup>c</sup> The “change in severity” includes both worsening and improvement of MDD.

MDD, major depressive disorder; RCT, randomized controlled trial.

## Quality assessment

**Supplementary Table 3. QA of cohort studies (Newcastle-Ottawa scale)**

	Selection			Comparability			Outcome	
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>
Almas 2015	a	a	c	b	b	c	a	d
Andersen 2005	b	a	c	a	b		a	c
Andersson 2015	a	a	a	a	b	b	a	d
Atasoy 2018	a	a	b	a	b	a	a	a
Atlantis 2012	a	a	b	b	b	c	a	b
Baggio 2015	b	a	b	b	b	a	a	b
Bangalore 2018	b	a	a	b	b	c	b	d
Begre 2008	a	a	b	a	b	c	a	b
Blasko 2010	a	a	b	a	b	b	a	c
Bowers 2013	a	a	a	a	a	b	a	a
Boyle 2010	a	a	b	a	a	b	a	c
Bremmer 2006	b	a	c	a	b	b	a	b
Brenner 2018	a	a	a	a	b	b	a	d
Brieler 2016	a	a	a	a	b	b	a	d
Briere 2014	a	a	b	a	b	a	a	c
Brunner 2014	a	a	c	b	b	b	a	a
Buderi 2019	b	a	a	a	c	b	a	d
Bulloch 2012	a	a	b	a	b	a	a	c
Butnoriene 2015	a	a	b	b	b	b	a	a

	Selection			Comparability			Outcome	
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>
Campayo 2010	a	a	b	a	b	c	a	c
Case 2018	a	a	b	a	b	b	b	d
Castilla Puentes 2019	a	a	a	b	c	b	a	d
Chen 2008	a	a	b	a	b	b	a	c
Coleman 2013	a	a	c	b	b	b	a	b
Connerney 2010	a	a	a	b	b	b	b	b
Dave 2011	a	a	b	b	b	d	a	d
Davidson 2010	b	a	b	b	b	c	b	b
Davis 2008	b	a	a	b	a	b	b	d
Davydow 2015	a	a	b	a	b	b	a	b
De Jonge 2006	a	a	b	a	b	a	a	d
Dickens 2008	b	a	b	b	b	b	a	b
Dirmaier 2010	a	a	a	a	b	a	a	a
Egede 2005	a	a	b	a	b	b	a	b
Eriksson 2008	b	a	a	a	b	a	a	c
Eriksson 2008	a	a	c	a	b	b	a	c
Frasure-Smith 2007	a	a	b	b	b	a	b	b
Frasure-Smith 2008	a	a	b	b	b	c	b	b



	Selection			Comparability			Outcome	
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>
Gallagher 2018	a	a	b	a	b	a	a	b
Ganguli 2006	a	a	b	a	b	b	a	b
Gasse 2014	a	a	a	a	b	b	a	b
Geerlings 2008	b	a	b	a	b	a	a	c
Gerra 2006	c	a	b	a	b	a	a	c
Goldbacher 2009	b	a	a	a	a	a	a	a
Goldstein 2015	a	a	b	b	b	c	a	d
Goodman 2008	b	a	b	a	b	a	a	a
Gracia-Garcia 2015	a	a	b	a	a	a	a	c
Graham 2019	a	a	b	a	b	b	a	a
Greenfield 2012	c	a	b	a	c	c	a	b
Gripp 2007	b	a	b	a	c	c	a	a
Groenvold 2007	c	a	b	a	b	a	a	a
Gross 2010	a	a	b	a	b	c	a	c
Hamano 2015	a	a	b	a	b	b	a	d
Heser 2013	a	a	b	a	b	b	a	b
Hiles 2016	a	a	b	a	b	a	a	c
Horberg 2008	a	a	a	a	b	b	a	d
Huffman 2008	a	a	b	a	b	a	b	b

	Selection			Comparability		Outcome		
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>
Janszky 2010	c	a	a	a	b	b	a	d
Johansson 2014	a	a	a	a	b	b	a	d
Josephson 2017	a	a	b	a	b	a	a	c
Karakus 2011	a	a	b	a	a	c	a	c
Katon 2010	a	a	b	a	b	b	a	a
Katon 2013	a	a	c	b	b	b	a	c
Katon 2015	a	a	a	a	b	a	a	a
Kendler 2009	c	a	b	b	a	b	a	d
Kivimaki 2010	a	a	a	a	b	b	a	a
Kohler 2013	c	a	b	a	b	a	a	b
Kohler 2015	a	a	b	a	b	a	a	d
Kuo 2006	b	a	b	a	b	a	a	d
Ladwig 2006	a	a	b	a	b	b	a	a
Landheim 2006	b	a	b	a	b	b	a	c
Lasserre 2014	a	a	b	a	b	a	a	b
Lasserre 2017	a	b	b	b	b	b	a	b
Lenoir 2011	a	a	b	a	b	a	a	c
Leventhal 2008	a	a	b	a	b	d	a	c
Liebetrau 2008	c	a	b	a	b	c	b	b
Lin 2009	a	a	b	b	b	a	a	b
Lin 2010	a	a	c	b	b	b	a	b
Linton 2005	b	a	b	a	b	c	a	b

	Selection			Comparability			Outcome		
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>	
Liu 2017	a	a	b	b	b	c	a	c	
Lloyd-Williams 2009	c	a	b	a	a	d	a	c	
Lo 2015	b	a	b	a	b	c	a	a	
Luppa 2013	a	a	b	a	b	a	a	c	
Mallon 2005	b	a	c	b	b	c	a	c	
Marijnissen 2014	b	a	c	a	b	b	a	c	
Martins 2012	a	a	b	a	b	a	a	c	
Mathur 2016	b	a	a	a	b	b	a	d	
May 2009	b	a	a	a	b	b	a	c	
McCarty 2009	b	a	b	a	a	a	a	b	
Melartin 2014	a	a	b	b	a	a	a	c	
Merikangas 2008	a	a	b	a	b	a	a	c	
Mezuk 2008a	a	a	b	a	b	b	a	c	
Mittag 2012	c	a	b	a	b	c	a	c	
Modgill 2012	a	a	b	a	b	c	a	c	
Mohamed 2019	a	a	a	b	b	b	a	a	
Mossaheb 2012	a	a	b	a	a	a	a	c	
Mulick 2019	c	b	c	a	b	b	a	b	
Mykletun 2007	a	a	c	a	b	b	b	b	
Nabi 2010	a	a	c	a	b	b	a	b	
Nicholl 2008	a	a	b	a	b	c	a	c	

	Selection			Comparability			Outcome	
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>
Nichols 2011	b	a	a	a	b	b	a	b
Nigatu 2015	a	a	b	b	b	b	b	b
Olfson 2017	a	a	b	b	b	a	a	b
Ossola 2018	a	a	b	b	b	b	b	b
Owora 2018	b	a	a	a	b	a	a	c
Pacek 2013	a	a	b	a	b	a	a	b
Pan 2010	b	a	c	a	b	b	a	b
Pan 2011a	c	a	c	a	b	c	a	c
Pan 2011b	b	a	c	a	b	c	b	b
Patel 2018	b	a	a	b	b	b	b	d
Patten 2008	a	a	b	a	b	c	a	c
Patten 2009a	a	a	b	a	b	c	a	c
Patten 2009b	a	a	b	a	b	c	a	c
Persoons 2005	a	a	b	a	c	a	a	b
Pintor 2006	c	a	b	a	c	a	a	c
Pirl 2008	c	a	b	a	c	a	a	a
Polanka 2017	a	a	b	a	b	c	b	b
Prince 2012	c	a	a	a	b	b	a	c
Reeves 2018	c	a	c	a	b	a	a	b
Richard 2013	c	a	b	a	b	a	a	c
Rollman 2012	c	a	b	a	b	c	a	a
Ryall 2007	a	a	b	a	b	c	a	b
Saha 2016	c	a	b	a	b	a	a	d
Saint Onge 2014	a	a	b	a	b	c	a	b

	Selection			Comparability			Outcome	
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>
Schmid 2011	a	a	b	a	b	c	a	b
Seldenrijk 2015	b	b	b	a	b	b	a	b
Sieu 2011	a	a	c	a	b	b	a	c
Simoes do Couto 2016	c	a	a	a	b	a	a	c
Surtees 2008a	a	a	b	a	b	b	a	b
Surtees 2008c	a	a	c	a	b	b	a	c
Suter 2011	b	a	b	a	b	c	a	c
Swanson 2013	a	a	b	a	b	c	a	c
Vallerand 2018	a	a	a	a	b	b	a	c
van den Broek 2011	c	a	b	a	b	a	a	c
van Marwijk 2015	a	a	b	a	b	c	b	b
Velly 2011	b	a	b	a	b	a	a	b
Vittengl 2018	b	a	c	b	c	c	b	c
Vodermaier 2017	a	a	b	a	b	b	a	a
Watson 2005	a	a	b	a	b	a	a	b
Whooley 2008	b	a	c	a	b	a	a	b
Willey 2010	a	a	c	a	b	b	a	c
Wilson 2011	c	a	b	a	b	a	a	c
Wilson 2016	c	a	b	a	b	a	a	b
Windle 2013	b	a	b	b	b	c	a	b

	Selection			Comparability			Outcome	
	Representativeness of the exposed cohort <sup>a</sup>	Selection of the non-exposed cohort <sup>b</sup>	Ascertainment of exposure <sup>c</sup>	Demonstration that outcome of interest was not present at start of study <sup>d</sup>	Comparability of cohorts on the basis of the design or analysis <sup>e</sup>	Assessment of outcome <sup>f</sup>	Was follow-up long enough for outcomes to occur <sup>g</sup>	Adequacy of follow up of cohorts <sup>h</sup>
Wium-Andersen 2019	a	a	a	a	b	b	a	a
Zambrana 2016	b	a	c	b	b	a	b	d

<sup>a</sup> a = truly representative of the average population in the community; b = somewhat representative of the average population in the community; c = selected group of users eg, nurses, volunteers.

<sup>b</sup> a = drawn from the same community as the exposed cohort; b = drawn from a different source.

<sup>c</sup> a = secure record (eg, medical or surgical records); b = structured interview; c = written self report.

<sup>d</sup> a = yes; b = no.

<sup>e</sup> a = study controls for the most important factor (age, sex, and/or ethnicity); b = study controls for most important AND any additional factor; c = no description or inadequate control.

<sup>f</sup> a = independent blind assessment; b = record linkage; c = self report; d = no description.

<sup>g</sup> a = yes; b = no.

<sup>h</sup> a = complete follow up - all subjects accounted for; b = subjects lost to follow up unlikely to introduce bias - small number lost (<20% or description of those lost); c = follow up rate <80% and no description of those lost; no statement.

QA, quality assessment.

#### Supplementary Table 4. QA of case-control studies (Newcastle-Ottawa scale)

	Selection			Comparability			Exposure	
	Is the case definition adequate? <sup>a</sup>	Representativeness of the cases <sup>b</sup>	Selection of controls <sup>c</sup>	Definition of controls <sup>d</sup>	Comparability of cases and controls on the basis of the design or analysis <sup>e</sup>	Ascertainment of exposure <sup>f</sup>	Same method of ascertainment for cases and controls <sup>g</sup>	Non-response rate <sup>h</sup>
Brommelhoff 2009	a	a	b	a	b	d	a	d
Brown 2005	b	a	a	a	b	d	a	a
Burton 2013	b	a	a	a	b	a	a	a
Empana 2006	b	a	a	a	b	a	a	d
Fang 2010	b	b	a	a	b	d	a	d

	Selection			Comparability			Exposure	
	Is the case definition adequate? <sup>a</sup>	Representativeness of the cases <sup>b</sup>	Selection of controls <sup>c</sup>	Definition of controls <sup>d</sup>	Comparability of cases and controls on the basis of the design or analysis <sup>e</sup>	Ascertainment of exposure <sup>f</sup>	Same method of ascertainment for cases and controls <sup>g</sup>	Non-response rate <sup>h</sup>
Farmer 2008	b	b	a	b	b	c	a	d
Herbst 2007	b	b	a	b	b	d	a	d
Inguva 2018	b	a	a	b	c	e	a	d
Jakobsen 2008	b	a	a	a	a	d	a	d
Janszky 2007	b	a	a	a	b	d	a	a
Levitan 2012	b	a	a	b	b	d	a	d
Niranjan 2012	b	a	a	a	b	d	a	a
Samaan 2009	b	b	a	a	c	b	a	d
Sawa 2014	b	a	b	b	b	a	a	a
Surtees 2008b	b	a	a	a	b	d	a	a

<sup>a</sup> a = yes, with independent validation; b = yes, eg, record linkage or based on self reports.

<sup>b</sup> a = consecutive or obviously representative series of cases; b = potential for selection biases or not stated.

<sup>c</sup> a = community controls; b = hospital controls.

<sup>d</sup> a = no history of disease (endpoint); b = no description of source.

<sup>e</sup> a = study controls for the most important factor (age, sex, and/or ethnicity); b = study controls for most important AND any additional factor; c = no description or inadequate control.

<sup>f</sup> a = secure record (eg, surgical records); b = structured interview where blind to case/control status; c = interview not blinded to case/control status; d = written self report or medical record only; e = no description.

<sup>g</sup> a = yes.

<sup>h</sup> a = same rate for both groups; d = no description.

QA, quality assessment.

**Supplementary Table 5. QA of cross-sectional studies (Newcastle-Ottawa scale)**

	Selection			Comparability	Outcome		
	Representativeness of the sample <sup>a</sup>	Sample size <sup>b</sup>	Non-respondents <sup>c</sup>	Ascertainment of the exposure (risk factor) <sup>d</sup>	The subjects in different outcome groups are comparable, based on the study design or analysis; confounding factors are controlled <sup>e</sup>	Assessment of outcome <sup>f</sup>	Statistical test <sup>g</sup>
Block 2016	a	a	a	a	b	b	b
Cannon-Spoor 2005	b	b	b	a	b	b	a
Delgado 2019	b	a	c	a	b	c	b
Dunn 2018	b	a	b	c	c	c	b
Grant 2016	b	a	a	a	b	c	a
Han 2016	b	a	a	a	b	a	a
Ivanovs 2018	b	a	c	a	c	b	b
Karpyak 2019	b	a	a	a	c	c	b
Martins 2009	b	a	a	a	b	c	a
Mather 2009	a	a	a	a	b	c	a
Mezuk 2015	c	a	a	a	b	c	a
Pisanu 2019	a	a	a	a	b	b	b
Shi 2014	b	a	a	a	b	c	a
Sintov 2009	a	a	a	a	b	c	a
Tietjen 2007	c	a	b	a	b	c	a

<sup>a</sup> a = truly representative of the average in the target population (all subjects or random sampling); b = somewhat representative of the average in the target population (nonrandom sampling); c = selected group of users eg, nurses, volunteers.

<sup>b</sup> a = justified and satisfactory; b = not justified.

<sup>c</sup> a = comparability between respondents and non-respondents characteristics is established, response rate is satisfactory; b = response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory; c = no description.

<sup>d</sup> a = validated measurement tool; c = no description of the measurement tool.

<sup>e</sup> b = study controls for most important AND any additional factor; c = no description or inadequate control



<sup>f</sup> a = independent blind assessment; b = record linkage; c = self report.

<sup>g</sup> a = statistical test used is clearly described and appropriate; measurement of the association is presented (including confidence intervals and p value); b = statistical test is not appropriate, not described, or incomplete.

QA, quality assessment.

**Supplementary Table 6. QA of meta-analysis studies (NICE scale)**

	Screening questions					Internal validity	External validity
	The review addresses an appropriate and clearly focused question that is relevant to the review question	The review collects the type of studies you consider relevant to the guidance review question	The literature search is sufficiently rigorous to identify all the relevant studies	Study quality is assessed and reported	An adequate description of the methodology used is included, and the methods used are appropriate to the question	Are the results internally valid? <sup>a</sup>	Are the results externally valid? <sup>a</sup>
Barlinn 2014	Yes	Yes	No	Yes	Yes	++	++
Bloch 2019	Yes	Yes	Yes	Yes	Yes	++	++
Charlson 2013	Yes	Yes	Yes	Yes	Yes	++	++
Correll 2017	Yes	Yes	Yes	Yes	Yes	++	++
Cosgrove 2008	Yes	Yes	Yes	Yes	Yes	++	++
de Wit 2010	Yes	Yes	Yes	No	Yes	++	++
Diniz 2013	Yes	Yes	No	Yes	Yes	++	+
Fan 2014	Yes	Yes	Yes	Yes	Yes	++	++
Leung 2012	Yes	Yes	Yes	Yes	Yes	++	++
Luppino 2010	Yes	Yes	Yes	Yes	Yes	++	++
Meijer 2011	Yes	Yes	Yes	Yes	Yes	++	++
Meng 2012	Yes	Yes	Yes	Yes	Yes	++	++
Mezuk 2008b	Yes	Yes	No	No	Yes	+	++
Nicholson 2006	Yes	Yes	No	No	Yes	++	++
Oerlemans 2007	Yes	Yes	Yes	No	Yes	++	++
Ownby 2006	Yes	Yes	Yes	Yes	Yes	++	++
Pinheiro 2015	Yes	Yes	Yes	Yes	Yes	++	++
Rotella 2013	Yes	Yes	No	No	Yes	++	++
Satin 2009	Yes	Unclear	Yes	No	Yes	+	++
Shi 2017	Yes	Yes	Yes	Yes	Yes	++	++
Van der Kooy 2007	Yes	Yes	Yes	Yes	Yes	++	++
van Dooren 2013	Yes	Yes	Yes	No	Yes	++	+
Vancampfort 2015	Yes	Yes	Yes	Yes	Yes	++	++

	Screening questions					Internal validity	External validity
	The review addresses an appropriate and clearly focused question that is relevant to the review question	The review collects the type of studies you consider relevant to the guidance review question	The literature search is sufficiently rigorous to identify all the relevant studies	Study quality is assessed and reported	An adequate description of the methodology used is included, and the methods used are appropriate to the question	Are the results internally valid? <sup>a</sup>	Are the results externally valid? <sup>a</sup>
Wang 2018	Yes	Yes	Yes	Yes	Yes	++	++
Wei 2019	Yes	Yes	Yes	Yes	Yes	++	++
Wu 2016 (Medicine)	Yes	Yes	Yes	Yes	Yes	++	++

<sup>a</sup> Studies are ranked as -, +, or ++ (low to high) based on the strength of internal or external validity. NICE, National Institute of Health and Care Excellence; QA, quality assessment.

## Included studies

**Supplementary Table 7. List of studies included in the review**

Author	Title	Journal	Year	Citation
Almas A; Forsell Y; Iqbal R; Janszky I; Moller J	Severity of depression, anxious distress and the risk of cardiovascular disease in a Swedish population-based cohort	PLoS One	2015	10(10):e0140742
Andersen K; Lolk A; Kragh-Sorensen P; Petersen NE; Green A	Depression and the risk of Alzheimer disease	Epidemiology	2005	16(2):233-38
Andersson NW; Gustafsson LN; Okkels N; Taha F; Cole SW; Munk-Jorgensen P; Goodwin RD	Depression and the risk of autoimmune disease: a nationally representative, prospective longitudinal study	Psychol Med	2015	45(16):3559-69
Atasoy S; Johar H; Fang XY; Kruse J; Ladwig KH	Cumulative effect of depressed mood and obesity on type II diabetes incidence: findings from the MONICA/KORA cohort study	J Psychosom Res	2018	115:66-70
Atlantis E; Shi Z; Penninx BJ; Wittert GA; Taylor A; Almeida OP	Chronic medical conditions mediate the association between depression and cardiovascular disease mortality	Soc Psychiatry Psychiatr Epidemiol	2012	47(4):615-625
Baggio S; Iglesias K; Studer J; Dupuis M; Daepfen JB; Gmel G	Is the relationship between major depressive disorder and self-reported alcohol use disorder an artificial one?	Alcohol	2015	50(2):195-99
Bangalore S; Shah R; Pappadopulos E; Deshpande CG; Shelbaya A; Prieto R; Stephens J; McIntyre RS	Cardiovascular hazards of insufficient treatment of depression among patients with known cardiovascular disease: a propensity score adjusted analysis	Eur Heart J	2018	4(4):258-66
Barlind K; Kepplinger J; Puetz V; Illigens BM; Bodechtel U; Siepmann T	Exploring the risk-factor association between depression and incident stroke: a systematic review and meta-analysis	Neuropsych Dis Treat	2014	11:1-14
Blasko I; Kemmler G; Jungwirth S; Wichart I; Krampal W; Weissgram S; Jellinger K; Tragl KH; Fischer P	Plasma amyloid beta-42 independently predicts both late-onset depression and Alzheimer disease	Am J Geriatr Psychiatry	2010	18(11):973-82
Bloch M; Meissner S; Nestler S	Does depression after stroke negatively influence physical disability? A systematic review and meta-analysis of longitudinal studies	J Affect Disorders	2019	247:45-56
Block A; Schipf S; Van der Auwera S; Hannemann A; Nauck M; John U; Volzke H; Freyberger HJ; Dorr M; Felix S; Zygumt M; Wallaschofski H; Grabe HJ	Sex- and age-specific associations between major depressive disorder and metabolic syndrome in two general population samples in Germany	Nord J Psychiat	2016	70(8):611-20
Bowers K; Laughon SK; Kim S; Mumford SL; Brite J; Kiely M; Zhang C	The association between a medical history of depression and gestational diabetes in a large multi-ethnic cohort in the United States	Paediatr Perinat Epidemiol	2013	27(4):323-28

Author	Title	Journal	Year	Citation
Boyle LL; Porsteinsson AP; Cui X; King DA; Lyness JM	Depression predicts cognitive disorders in older primary care patients	J Clin Psychiatry	2010	71(1):74-79
Bremmer MA; Hoogendijk WJG; Deeg DJH; Schoevers RA; Schalk BWM; Beekman ATF	Depression in older age is a risk factor for first ischemic cardiac events	Am J Geriatr Psychiatry	2006	14(6):523-30
Brenner P; Hägg D; Bodén R; Li G; DiBernardo A; Brandt L; Reutfors J	Treatment-resistant depression as a risk factor for substance use disorders: a national register-based cohort study	APA	2018	6(75)
Brieler JA; Lustman PJ; Scherrer JF; Salas J; Schneider FD	Antidepressant medication use and glycaemic control in co-morbid type 2 diabetes and depression	Fam Pract	2016	33(1):30-36
Briere FN; Rohde P; Seeley JR; Klein D; Lewinsohn PM	Comorbidity between major depression and alcohol use disorder from adolescence to adulthood	Compr Psychiatry	2014	55(3):526-33
Brommelhoff JA; Gatz M; Johansson B; McArdle JJ; Fratiglioni L; Pedersen NL	Depression as a risk factor or prodromal feature for dementia? Findings in a population-based sample of Swedish twins	Psychol Aging	2009	24(2):373-84
Brown LC; Majumdar SR; Newman SC; Johnson JA	History of depression increases risk of Type 2 diabetes in younger adults	Diabetes Care	2005	28(5):1063-67
Brunner EJ; Shipley MJ; Britton AR; Stansfeld SA; Heuschmann PU; Rudd AG; Wolfe CDA; Singh-Manoux A; Kivimaki M	Depressive disorder, coronary heart disease, and stroke: dose-response and reverse causation effects in the Whitehall II cohort study	Eur J Prev Cardiol	2014	21(3):340-46
Bulloch A; Lavorato D; Williams J; Patten S	Alcohol consumption and major depression in the general population: the critical importance of dependence	Depress Anxiety	2012	29(12):1058-64
Burton C; Campbell P; Jordan K; Strauss V; Mallen C	The association of anxiety and depression with future dementia diagnosis: a case-control study in primary care	Fam Pract	2013	30(1):25-30
Butnorieni J; Bunevicius A; Saudargiene A; Nemeroff CB; Norkus A; Cicieniene V; Bunevicius R	Metabolic syndrome, major depression, generalized anxiety disorder, and ten-year all-cause and cardiovascular mortality in middle aged and elderly patients	Int J Cardiol	2015	190:360-66
Campayo A; de Jonge P; Roy JF; Saz P; de la Camara C; Quintanilla MA; Marcos G; Santabarbara J; Lobo A	Depressive disorder and incident diabetes mellitus: the effect of characteristics of depression	Am J Psychiatry	2010	167(5):580-88
Cannon-Spoor HE; Levy JA; Zubenko GS; Zubenko WW; Cohen RM; Mirza N; Putnam K; Sunderland T	Effects of previous major depressive illness on cognition in Alzheimer disease patients	Am J Geriatr Psychiatry	2005	13(4):312-18
Case SM; Sawhney M; Stewart JC	Atypical depression and double depression predict new-onset cardiovascular disease in U.S. adults	Depress Anxiety	2018	35(1):10-17
Castilla Puentes RC	Mood and anxiety disorders in patients with Alzheimer disease (AD): results of a cohort study using U.S. claims databases	APA	2019	4(180)

Author	Title	Journal	Year	Citation
Charlson FJ; Moran AE; Freedman G; Norman RE; Stapelberg NJC; Baxter AJ; Vos T; Whiteford HA	The contribution of major depression to the global burden of ischemic heart disease: a comparative risk assessment	BMC Med	2013	11:250
Chen R; Hu Z; Wei L; Qin X; McCracken C; Copeland JR	Severity of depression and risk for subsequent dementia: cohort studies in China and the UK	Br J Psychiatry	2008	193(5):373-77
Coleman SM; Katon W; Lin E; Von Korff M	Depression and death in diabetes; 10-year follow-up of all-cause and cause-specific mortality in a diabetic cohort	Psychosomatics	2013	54(5):428-36
Connerney I; Sloan RP; Shapiro PA; Bagiella E; Seckman C	Depression Is associated with increased mortality 10 years after coronary artery bypass surgery	Psychosom Med	2010	72(9):874-81
Correll CU; Solmi M; Veronese N; Bortolato B; Rosson S; Santonastaso P; Thapa-Chhetri N; Fornaro M; Gallicchio D; Collantoni E; Pigato G; Favaro A; Monaco F; Kohler C; Vancampfort D; Ward PB; Gaughran F; Carvalho AF; Stubbs B	Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls	World Psychiatry	2017	16(2):163-80
Cosgrove MP; Sargeant LA; Griffin SJ	Does depression increase the risk of developing type 2 diabetes?	Occup Med	2008	58(1):7-14
Dave DM; Tennant J; Colman G	Isolating the effect of major depression on obesity: role of selection bias	J Ment Health Policy	2011	14(4):165-86
Davidson KW; Burg MM; Kronish IM; Shimbo D; Dettenborn L; Mehran R; Vorchheimer D; Clemow L; Schwartz JE; Lesperance F; Rieckmann N	Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome	Arch Gen Psychiatry	2010	67(5):480-88
Davis J; Fujimoto RY; Juarez DT; Hodges KA; Asam JK	Major depression associated with rates of cardiovascular disease state transitions	Am J Manag Care	2008	14(3):125-29
Davydow DS; Levine DA; Zivin K; Katon WJ; Langa KM	The association of depression, cognitive impairment without dementia, and dementia with risk of ischemic stroke: a cohort study	Psychosom Med	2015	77(2):200-08
de Jonge P; van den Brink RHS; Spijkerman TA; Ormel J	Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events	J Am Coll Cardiol	2006	48(11):2204-8
de Wit L; Luppino F; van Straten A; Penninx B; Zitman F; Cuijpers P	Depression and obesity: a meta-analysis of community-based studies	Psychiatr Res	2010	178(2):230-35
Delgado M; Ng CK; Seidel R; Castro G; Barengo N	Relationship between depression and disability in adults with arthritis: analysis of 2015 BRFSS data	APA	2019	4(61)
Dickens C; McGowan L; Percival C; Tomenson B; Cotter L; Heagerty A; Creed F	New onset depression following myocardial infarction predicts cardiac mortality	Psychosom Med	2008	70(4):450-55
Diniz BS; Butters MA; Albert SM; Dew MA; Reynolds CF	Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies	Br J Psychiatry	2013	202(5):329-35

Author	Title	Journal	Year	Citation
Dirmaier J; Watzke B; Koch U; Schulz H; Lehnert H; Pieper L; Wittchen HU	Diabetes in primary care: prospective associations between depression, nonadherence and glycemic control	Psychother Psychosom	2010	79(3):172-78
Dunn TJ; Korgaonkar S; Ramachandran S	The association between prescription stimulant use and prescription drug misuse	ISPOR	2018	05:PMH53
Egede LE; Nietert PJ; Zheng D	Depression and all-cause and coronary heart disease mortality among adults with and without diabetes	Diabetes Care	2005	28(6):1339-45
Empana JP; Jouven X; Lemaitre RN; Sotoodehnia N; Rea T; Raghunathan TE; Simon G; Siscovick DS	Clinical depression and risk of out-of-hospital cardiac arrest	Arch Intern Med	2006	166:195-200
Eriksson AK; Ekblom A; Granath F; Hilding A; Efendic S; Ostenson CG	Psychological distress and risk of prediabetes and Type 2 diabetes in a prospective study of Swedish middle-aged men and women.	Diabet Med	2008	25(7):834-42
Fan H; Yu W; Zhang Q; Cao H; Li J; Wang J; Shao Y; Hu X	Depression after heart failure and risk of cardiovascular and all-cause mortality: a meta-analysis	Prev Med	2014	63:36-42
Fang F; Xu Q; Park Y; Huang X; Hollenbeck A; Blair A; Schatzkin A; Kamel F; Chen H	Depression and the subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study	Mov Disord	2010	25(9):1157-62
Farmer A; Korszun A; Owen MJ; Craddock N; Jones L; Jones I; Gray J; Williamson RJ; McGuffin P	Medical disorders in people with recurrent depression	Br J Psychiatry	2008	192(5):351-55
Frasere-Smith N; Lesperance F	Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease	Arch Gen Psychiatry	2008	65(1):62-71
Frasere-Smith N; Lesperance F; Irwin MR; Sauve C; Lesperance J; Theroux P	Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes	Biol Psychiatry	2007	62(4):302-8
Gallagher D; Kiss A; Lanctot K; Herrmann N	Depression and risk of Alzheimer dementia: a longitudinal analysis to determine predictors of increased risk among older adults with depression	Am J Geriatr Psychiatry	2018	26(8):819-27
Ganguli M; Du Y; Dodge HH; Ratcliff GG; Chang CC	Depressive symptoms and cognitive decline in late life: a prospective epidemiological study	Arch Gen Psychiatry	2006	63(2):153-60
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Surtees PG; Wainwright NWJ; Luben RN; Wareham NJ; Bingham SA; Khaw KT	Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study	Am J Psychiatry	2008c	165(4):515-523
Swanson SA; Zeng Y; Weeks M; Colman I	The contribution of stress to the comorbidity of migraine and major depression: results from a prospective cohort study	BMJ Open	2013	3:e002057
Tietjen GE; Peterlin B; Brandes JL; Hafeez F; Hutchinson S; Martin VT; Dafer RM; Aurora SK; Stein MR; Herial NA; Utley C; White L; Khuder SA	Depression and anxiety: effect on the migraine-obesity relationship	Headache	2007	47(6):866-875
Vallerand IA; Lewinson RT; Frolkis AD; Lowerison MW; Kaplan GG; Swain MG; Bulloch AGM; Patten SB; Barnabe C	Depression as a risk factor for the development of rheumatoid arthritis: a population-based cohort study	RMD Open	2018	4(2):e000670
van den Broek KC; deFilippi CR; Christenson RH; Seliger SL; Gottdiener JS; Kop WJ	Predictive value of depressive symptoms and B-type natriuretic peptide for new-onset heart failure and mortality	Am J Cardiol	2011	107(5):723-29
Van der Kooy K; van Hout H; Marwijk H; Marten H; Stehouwer C; Beekman A	Depression and the risk for cardiovascular diseases: systematic review and meta analysis	Int J Geriatr Psych	2007	22(7):613-26
van Dooren FEP; Nefs G; Schram MT; Verhey FRJ; Denollet J; Pouwer F	Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis	PLoS One	2013	8(3):e57058
van Marwijk HWJ; van der Kooy KG; Stehouwer CDA; Beekman ATF; van Hout HPJ	Depression increases the onset of cardiovascular disease over and above other determinants in older primary care patients, a cohort study	BMC Cardiovasc Disor	2015	15:40
Vancampfort D; Mitchell AJ; De Hert M; Sienaert P; Probst M; Buys R; Stubbs B	Type 2 diabetes in patients with major depressive disorder: a meta-analysis of prevalence estimates and predictors	Depress Anxiety	2015	32(10):763-73
Velly AM; Look JO; Carlson C; Lenton PA; Kang W; Holcroft CA; Friction JR	The effect of catastrophizing and depression on chronic pain - a prospective cohort study of temporomandibular muscle and joint pain disorders	Pain	2011	152(10):2377-83
Vittengl JR	Mediation of the bidirectional relations between obesity and depression among women	Psychiatr Res	2018	264:254-59

Author	Title	Journal	Year	Citation
Vodermaier A; Lucas S; Linden W; Olson R	Anxiety after diagnosis predicts lung cancer-specific and overall survival in patients with Stage III non-small cell lung cancer: a population-based cohort study	J Pain Symptom Manag	2017	53(6):1057-65
Wang S; Mao S; Xiang D; Fang C	Association between depression and the subsequent risk of Parkinson's disease: a meta-analysis	Prog Neuro-Psychopharmacol Biol Psychiatry	2018	86:186-92
Watson M; Homewood J; Haviland J; Bliss JM	Influence of psychological response on breast cancer survival: 10-year follow-up of a population-based cohort	Eur J Cancer	2005	41(12):1710-14
Wei J; Hou R; Zhang X; Xu H; Xie L; Chandrasekar EK; Ying M; Goodman M	The association of late-life depression with all-cause and cardiovascular mortality among community-dwelling older adults: systematic review and meta-analysis	Br J Psychiatry	2019	215(2):449-55
Whooley MA; de Jonge P; Vittinghoff E; Otte C; Moos R; Carney RM; Ali S; Dowray S; Na B; Feldman MD; Schiller NB; Browner WS	Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease	JAMA	2008	300(20):2379-88
Willey JZ; Disla N; Moon YP; Paik MC; Sacco RL; Boden-Albala B; Elkind MSV; Wright CB	Early depressed mood after stroke predicts long-term disability: the Northern Manhattan Stroke Study (NOMASS)	Stroke	2010	41:1896-1900
Wilson RS; Begeny CT; Boyle PA; Schneider JA; Bennett DA	Vulnerability to stress, anxiety, and development of dementia in old age	Am J Geriatr Psychiatry	2011	19(4):327-34
Wilson RS; Boyle PA; Capuano AW; Shah RC; Hoganson GM; Nag S; Bennett DA	Late-life depression is not associated with dementia-related pathology	Neuropsychology	2016	30(2):135-42
Windle M; Windle RC	Recurrent depression, cardiovascular disease, and diabetes among middle-aged and older adult women	J Affect Disorders	2013	150(3):895-902
Wium-Andersen MK; Wium-Andersen IK; Prescott EIB; Overvad K; Jorgensen MB; Osler M	An attempt to explain the bidirectional association between ischaemic heart disease, stroke and depression: a cohort and meta-analytic approach	Br J Psychiatry	2019	:1-8
Wu Q; Kling JM	Depression and the risk of myocardial infarction and coronary death: a meta-analysis of prospective cohort studies	Medicine	2016	95(6):e2815
Wulsin L; Alwell K; Moomaw CJ; Lindsell CJ; Kleindorfer DO; Woo D; Flaherty ML; Khatri P; Adeoye O; Ferioli S; Broderick JP; Kissela BM	Comparison of two depression measures for predicting stroke outcomes	J Psychosom Res	2012	72(3):175-79
Zambrana RE; Lopez L; Dinwiddie GY; Ray RM; Eaton CB; Phillips LS; Wassertheil-Smoller S	Association of baseline depressive symptoms with prevalent and incident pre-hypertension and hypertension in postmenopausal Hispanic women: results from the Women's Health Initiative	PLoS One	2016	11(4):e0152765



## Cancer

**Supplementary Table 8. Summary of studies assessing the association between depression and cancer incidence**

Study, N	Depression definition	Estimate; time period	Cancer type	Impact of depression on comorbidity	
				Presence of depression	Depression recurrence/severity
Gross 2010 (Baltimore ECA) (N = 3177)	DIS diagnosis of MDE	HR (95% CI) for incidence of cancer according to history of MDE; 24-year follow-up <sup>a</sup>	Any	Adjusted: <b>1.87 (1.16-3.01)<sup>b</sup></b> Unadjusted: 1.15 (0.75-1.78)	NR
			Breast	Any: 3.38 (0.83-13.76); p = 0.08 Single episode: 2.14 (0.31-14.76)	Recurrent: 2.03 (0.25-16.13) Symptom count: 1.15 (0.99-1.34); p = 0.06
			Colon	Any: 4.31 (0.71-26.18) Single: no cases	Recurrent: no cases Symptom count: 0.97 (0.75-1.25)
			Lung	Any: 0.82 (0.25-2.64) Single: no cases	Recurrent: no cases Symptom count: 0.97 (0.84-1.12)
			Prostate	Any: 1.09 (0.14-8.73) Single: <b>6.88 (1.98-23.90)</b>	Recurrent: no cases Symptom count: 1.03 (0.83-1.29)
			Skin	Any: 1.71 (0.38-7.68) Single: no cases	Recurrent: 5.43 (0.72-41.12) Symptom count: 1.02 (0.78-1.33)
			Any	0.92 (0.54-1.56); p = 0.75	NR
Karakus 2011 (Health and Retirement Study) (N = 3645)	8-item CES-D ≥3	OR (95% CI) for incidence of cancer according to depression at baseline; 12-year follow-up <sup>c</sup>	Any		
Reeves 2018 (Nurses' Health Study I and II) (N = 66,692 and 89,820)	Self-report of clinical diagnosis; MHI-5 <52 defined severe symptoms	HR (95% CI) for cumulative number of times reported clinical depression diagnosis at each 2-year cycle; 10- or 12-year study period <sup>d</sup>	Breast	1 episode: 0.99 (0.87-1.12)	<u>Any depression</u> 2 episodes: 1.05 (0.85-1.29) ≥3 episodes: 1.13 (0.85-1.49)
					<u>Severe depressive symptoms</u> 1 episode: 0.90 (0.79-1.02) 2 episodes: 0.95 (0.68-1.32) ≥3 episodes: 0.86 (0.63-1.17)
<b>Meta-analysis</b>					
Oerlemans 2007 Meta-analysis (N = 127,840)	Any validated measures of depression or questionnaires that resemble DSM criteria for MDD	RR (95% CI) for pooled estimate of covariate-adjusted individual estimates	Any	1.12 (0.99-1.26)	NR
			Breast	1.59 (0.74-3.44)	NR
			Lung	1.37 (0.88-2.16)	NR
			Prostate	1.60 (0.40-6.50)	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, smoking status, parity (breast cancer only).

<sup>b</sup> Adjusted for age, sex, ethnicity, marital status, smoking status, baseline socioeconomic status, alcohol abuse/dependence; in a subgroup analysis that excluded 145 respondents who at baseline rated their health status as poor, 24 of whom had a lifetime history of MDE; MDE was no longer statistically significantly associated with an increased cancer hazard (HR 1.56; 95% CI: 0.90-2.70).

<sup>c</sup> Adjusted for age at baseline, sex, race, marital status, education level, BMI, cigarette smoking, functional limitations index, self-report of limited ability to work, household income.

<sup>d</sup> Adjusted for age, calendar year, BMI, count of antidepressant use, age at menarche, current oral contraceptive use (Nurses' Health Study II only), type of postmenopausal hormone therapy use, age at menopause, age at first birth and parity, history of biopsy-confirmed benign breast disease, family history of breast cancer, mammogram in prior 2 years, smoking status, physical activity, alcohol intake, and Alternative Healthy Eating Index score.

BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECA, Epidemiologic Catchment Area; HR, hazard ratio; MDD, major depressive disorder; MDE, major depressive episode; MHI, Mental Health Inventory; NR, not reported; OR, odds ratio; RR, risk ratio.

**Supplementary Table 9. Summary of studies assessing the association between depression and cancer severity**

Study	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
<b>Any cancer – population cohorts</b>				
Coleman 2013, Lin 2009 (Pathways Epidemiologic Study) (N = 4623)	PHQ-9 diagnosis of MDD	HR (95% CI) for mortality; 10-year follow-up <sup>a</sup>	<u>Cancer mortality, MDD</u> 5 years: 1.27 (0.77-2.10) 10 years: 1.0 (0.65-1.53)	<u>Cancer mortality, minor depression</u> 5 years: 0.94 (0.53-1.68) 10 years: 0.82 (0.50-1.36)
Mykletun 2007 (HUNT-2) (N = 61,349)	HADS ≥8	OR (95% CI) for cancer mortality; mean 4.4-year follow-up <sup>b</sup>	Case-level depression: <b>1.33 (1.05-1.69); p &lt; 0.05</b>	Continuous HADS scale score: 1.09 (0.98-1.22) <sup>c</sup>
Saint Onge 2014 (NHIS) (N = 11,369)	CIDI-SF diagnosis of MDD	HR (95% CI) for cancer mortality; 7-year follow-up <sup>d</sup>	<u>Baseline cancer status</u> All: <b>2.49 (1.64-3.79); p ≤ 0.001</b> No cancer: 1.76 (0.89-3.49); p ≤ 0.10 Cancer: 1.19 (0.32-4.40)	NR
<b>Any cancer – terminally ill patients</b>				
Gripp 2007 (N = 216)	HADS >10	HR (95% CI) for cancer survival; 6- month follow-up	<b>0.27 (0.15-0.41); adjusted p = 0.0006<sup>e</sup></b>	NR
Lloyd-Williams 2009 (N = 87)	EPDS >13	HR (95% CI) for OS per 1-point increase in EDS adjusted for age; 12-month follow- up <sup>f</sup>	NR	Overall: <b>1.07 (1.01-1.16); p &lt; 0.05</b> <u>Subscales</u> Pain: 1.03 (0.94-1.04) Mood: 0.93 (0.82-1.06) Sickness: 1.01 (0.91-1.10) Breathless: <b>1.15 (1.04-1.29); p &lt; 0.01</b> Movement: 1.01 (0.91-1.13) Quality of Life: 1.01 (0.88-1.16) Tiredness: <b>1.15 (1.02-1.33); p &lt; 0.05</b>
<b>Any cancer – meta-analysis</b>				
Satin 2009 (N = 2097 [progression] and 9417 [mortality])	Depressive symptoms or a diagnosis of major or minor depressive episode	RR or HR (95% CI) for depressive symptoms or clinical diagnosis and cancer	<u>Cancer recurrence (RR)</u> Depressive symptoms: 1.23 (0.85-1.77); p = 0.275 <u>Cancer mortality (HR)</u> Clinical depression: 1.67 (0.96-2.90); p = 0.07	NR

Study	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
			Depressive symptoms: <b>1.09 (1.03-1.15)</b> ; <b>p = 0.003</b>	
<b>Breast cancer</b>				
Groenvold 2007 (BCCG 89 Program) (N = 1588)	HADS ≥8 and ≥11	RR (95% CI) for RFS and OS for dichotomized HADS scores; median 13-year follow-up <sup>g</sup>	NR	<u>RFS by HADS score</u> ≥8 vs. <8: 1.19 (0.95-1.50); p = 0.1367 ≥11 vs. <11: 1.13 (0.79-1.62); p = 0.5018 <u>OS by HADS score</u> ≥8 vs. <8: 1.17 (0.92-1.49); p = 0.2100 ≥11 vs. <11: 1.17 (0.81-1.68); p = 0.4162
Watson 2005 (N = 578)	HADS ≥8 and ≥11	HR (95% CI) for DFS or mortality by HADS score (vs. ≤7); 10-year follow-up <sup>h</sup>	NR	<u>DFS by HADS score</u> 0-7: reference 8-10: 0.70 (0.36-1.39) ≥11: 1.74 (0.70-4.33) <u>Mortality by HADS score</u> 0-7: reference 8-10: 0.69 (0.34-1.40) ≥11: 2.43 (0.97-6.10)
<b>NSCLC</b>				
Pirl 2008 (EIPC) (N = 43)	HADS ≥8	OR (95% CI) or HR (95% CI) for baseline depression and mortality; 30-month follow-up <sup>i</sup>	6-month mortality: <b>OR 5.30 (1.04-26.88)</b> ; <b>p = 0.04<sup>i</sup></b> Overall mortality: HR 1.89 (0.88-4.06); p = 0.10 <sup>k</sup>	NR
Vodermaier 2017 (N = 684)	PSSCAN ≥11	HR (95% CI) for mortality; median 64.5-month follow-up <sup>l</sup>	Lung cancer mortality: 1.02 (0.99-1.05); p = 0.157 All-cause mortality: 1.02 (0.99-1.05); p = 0.133	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, race, education, marital status, diabetes duration, treatment intensity, medical comorbidity, hypertension diagnosis, BMI, smoking, limited physical activity, and glycated hemoglobin.

<sup>b</sup> Adjusted for age and sex, plus any of the following that were determined to be confounding when added individually: somatic symptoms/diagnoses, physical impairment, health-related behaviors (smoking, alcohol problems, and physical activity), educational level and socioeconomic status, physical measurements (BMI, DBP, total cholesterol).

<sup>c</sup> Significant at lower level of adjustment only.

<sup>d</sup> Adjusted for year of birth, ethnicity, sex, foreign birth, marital status, education, employment status, logged family income, alcohol consumption, physical activity, smoking.

<sup>e</sup> Univariate analysis; no longer significant when entered in the multivariate analysis (data NR).

<sup>f</sup> Adjusted for age.

<sup>g</sup> Adjusted for menopause status, estrogen receptor status, histology and grade, tumor size, number of positive lymph nodes, age, adjuvant therapy, surgery type, age-chemotherapy interaction.

<sup>h</sup> Adjusted for histopathological grade, number of positive lymph nodes, pathological tumor size, type of surgery, treatment with radiotherapy, chemotherapy and/or endocrine therapy, estrogen receptor status, and age.

<sup>i</sup> Multivariate analysis included HADS  $\geq 8$  and ECOG Performance Status.

<sup>j</sup> Logistic regression analysis of mortality predictors.

<sup>k</sup> Cox regression analysis.

<sup>l</sup> Adjusted for age, sex, marital status, ethnicity, employment status, performance status, stage, histology, and treatment variables.

BMI, body mass index; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; DBCG, Danish Breast Cancer Cooperative Group; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; DBP, diastolic blood pressure; EPDS, Edinburgh Postnatal Depression Scale; EIPC, Impact of Early Intervention with Palliative Care on Quality of Life in Patients with Advanced NSCLC; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; HUNT, Health Study of Nord-Trøndelag County, Norway; MDD, major depressive disorder; NHIS, National Health Interview Survey; NSCLC, non-small cell lung cancer; NR, not reported; OR, odds ratio; OS, overall survival; PHQ, Patient Health Questionnaire; PSSCAN, Psychosocial Screen for Cancer; RFS, recurrence-free survival; RR, risk ratio.

## CNS

### Dementia and Alzheimer disease

**Supplementary Table 10. Summary of studies assessing the association between depression and CNS disorder incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
<i>Dementia only</i>				
Boyle 2010 (N = 470)	DSM-IV MDD criteria assessed using SCID	HR (95% CI) for incident dementia or cognitive disorder NOS; 3-year follow-up <sup>a</sup>	MDD: <b>3.68 (2.1-6.42)</b>	Per 1-unit increase in HAM-D: <b>1.07 (1.02-1.12)</b> Per 1-unit increase in HAM-D psychological-affective items: <b>1.11 (1.02-1.21)</b> Minor depression: <b>1.84 (1.05-3.21)</b>
Burton 2013 (CiPCA) (N = 1753)	Diagnostic Read codes	OR (95% CI) for incident dementia; 8-year period <sup>b</sup>	Overall: <b>2.54 (1.39-4.63)</b> Female: <b>2.95 (2.07-4.22)</b> Male: <b>5.91 (1.98-17.6)</b>	NR
Chen 2008 (MRC-Alpha) (N = 3341)	GMS-AGECAT ≥3	HR (95% CI) for incident dementia at 2 and 4 years according to level of depression at baseline; 4-year follow-up <sup>c</sup>	<u>Level 4 depression score vs. 0, year 2 and 4 combined</u> Men: 1.73 (0.61-4.91) Women: <b>2.07 (1.03-4.15)</b> ; p = 0.78 vs. men With CVD comorbidities: 1.47 (0.44-4.86) Without CVD comorbidities: <b>2.17 (1.12-4.22)</b> ; p = 0.58 vs. CVD comorbidities With depressive neurosis: <b>2.77 (1.22-6.26)</b> With depressive psychosis: 1.66 (0.78-3.53); p = 0.37 vs. depressive neurosis Age 65-74: <b>6.10 (1.92-19.4)</b> Age 75-84: 2.16 (0.92-5.08) Age ≥85: 1.05 (0.45-1.94); p = 0.012 vs. 65-74	<u>Incidence at 2/4 years according to depression level</u> 0 (no depression): reference 1 (sub-case): 1.57 (0.95-2.61)/1.34 (0.77-2.34) 2 (sub-case): 0.79 (0.44-1.43)/0.55 (0.25-1.21) 3 (case-level): 0.95 (0.52-1.71)/0.85 (0.43-1.68) 4 (case-level): <b>2.13 (1.12-4.06)</b> ; p ≤ 0.05/2.45 ( <b>1.17-5.15</b> ); p ≤ 0.05
Ganguli 2006 (Monongahela Valley Independent Elders Survey) (N = 1265)	Modified CES-D ≥5	Effect estimate for the association of depression with cognitive scores; mean 7.4-year follow-up	<u>Association with baseline cognitive scores in patients who developed eventual dementia</u> Learning: -0.134; p = NS Memory: <b>-0.246</b> ; p = <b>0.047</b> Language: -0.161; p = NS Visuospatial ability: <b>-0.178</b> ; p = <b>0.02</b> Executive: <b>-0.231</b> ; p = <b>0.01</b>	Depression was associated with baseline scores on all composites and the MMSE, but not with decline on any, regardless of whether depression was transient or persistent (data NR)

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
			MMSE: -0.065; p = NS <u>Association with cognitive scores over time in patients who developed eventual dementia</u> Learning: 0.001; p = NS Memory: 0.038; p = NS Language: 0.023; p = NS Visuospatial ability: -0.006; p = NS Executive: 0.036; p = NS MMSE: 0.018; p = NS	
Kohler 2015 (N = 35,791)	ICPC code	HR (95% CI) for incident dementia; 12-year follow-up <sup>e</sup>	<u>Interaction with hypertension</u> Depression: <b>1.84 (1.31-2.58); p &lt; 0.001</b> Depression + hypertension: <b>2.40 (1.58-3.64); p &lt; 0.001</b> <u>Interaction with stroke</u> Depression only: <b>1.89 (1.39-2.56); p &lt; 0.001</b> Depression and stroke: <b>2.60 (1.54-4.38); p &lt; 0.001</b>	NR
Luppa 2013 (LEILA 75+) (N = 888)	DSM-III-R MDD criteria assessed using SCID; CES-D ≥23	HR (95% CI) for incident dementia; 8-year follow-up <sup>f</sup>	<b>2.75 (1.01-7.50); p = 0.048</b>	Total CES-D score: 0.99 (0.97-1.02); p = 0.590 <u>Per 1-point increase</u> CES-D at baseline: 1.00 (0.98-1.02); p = 0.629 Mood-related symptoms: 1.00 (0.94-1.06), p = 0.956 Motivation-related symptoms: 1.00 (0.90-1.10); p = 0.951
Simoès do Couto 2016 (N = 644)	DSM-V MDD criteria assessed using AMDP-System	OR (95% CI) for incident dementia; 25-year follow-up <sup>a</sup>	All: <b>3.36 (1.76-6.80); p &lt; 0.0001</b> Age <45: <b>8.69 (2.21-34.23)</b> Age <60: <b>4.00 (1.87-8.60)</b> Depression onset <60 years: 0.72 (0.30-1.74) Follow-up >10 years: <b>4.16 (1.96-8.83)</b>	NR
Wilson 2016 (N = 785)	DSM-III MDD criteria assessed using DIS	OR (95% CI) for incident dementia; mean 8-year follow-up <sup>a</sup>	Depression: <b>2.358 (1.641-3.388)</b>	Elevated depressive symptoms: <b>1.975 (1.356-2.874)</b>

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
<b><i>Alzheimer disease only</i></b>				
Andersen 2005 (N = 3086)	Participant interview	OR (95% CI) for history of depression; 5-year follow-up <sup>a</sup>	<u>Overall</u> Baseline: 1.7 (1.0-2.7) 2-year follow-up: 1.8 (1.0-3.3) 5-year follow-up: 1.6 (0.9-2.7) <u>1 episode of depression</u> Baseline: 1.3 (0.6-2.6) 2-year follow-up: 1.5 (0.7-3.3) 5-year follow-up: 1.4 (0.7-2.8)	<u>≥2 episodes of depression</u> Baseline: <b>2.7 (1.1-6.6)</b> 2-year follow-up: <b>4.8 (1.9-12.5)</b> 5-year follow-up: 1.9 (0.6-5.9)
Blasko 2010, Mossaheb 2012 (VITA) (N = 331)	DSM-IV MDD criteria assessed using SCID	OR (95% CI) for incident Alzheimer disease; 5-year follow-up	<u>Individual MDD symptoms at baseline</u> Depressed mood: 1.57 (0.77-3.23); p = 0.21 Loss of interest: 2.80 (0.97-8.08); p = 0.05747 Change of appetite: 3.40 (0.35-32.94); p = 0.29 Sleep disturbance: 1.35 (0.87-2.1); p = 0.18 Psychomotor change: <b>2.67 (1.13-6.28);</b> <b>p = 0.024</b> Loss of energy: <b>2.15 (1-4.6); p = 0.049</b> Worthlessness: 1.12 (0.22-5.63); p = 0.89 Concentration difficulty: 2.22 (0.97-5.09); p = 0.06014	<u>According to short-form GDS<sup>g</sup></u> Including MCI at baseline: 1.2 (1.0-1.4); p = 0.064 No MCI at baseline: 1.2 (1.0-1.5); p = 0.084
Castilla Puentes 2019 (N = 432,229)	MedDRA Lowest Level Term	OR (95% CI) for incident Alzheimer disease following any depression diagnosis; time frame and covariate adjustment NR	Current depression episode: <b>2.07 (1.92-2.23)</b> Single episode MDE: <b>1.55 (1.51-1.59)</b>	All recurrent MDE: <b>4.75 (4.39-5.14)</b> Mild recurrent MDE: <b>1.98 (1.92-2.05)</b> Moderate recurrent MDE: <b>1.62 (1.59-1.66)</b> Severe single MDE with psychotic features: <b>3.35 (3.15-3.55)</b> Severe recurrent MDE without psychotic features: <b>1.58 (1.53-1.63)</b>
Gallagher 2018 (NACC database) (N = 1965)	DSM MDD criteria assessed using UDS Form A5	HR (95% CI) for incident Alzheimer disease; median 27-month follow-up <sup>h</sup>	<b>1.44 (1.16-1.79); p &lt; 0.001</b>	Total GDS score: 0.98 (0.96-1.01) GDS >5 (clinical depression): 0.87 (0.72-1.05)



Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Gracia-Garcia 2015 (ZARADEMP) (N = 3864)	GMS-AGECAT ≥3	HR (95% CI) for incident Alzheimer disease; 5-year follow-up <sup>i</sup>	All depression: 1.11 (0.57-2.15); p = 0.750 First-ever episode: 1.20 (0.60-2.40); p = 0.610 Depression only at baseline: 1.53 (0.54-4.39); p = 0.420 Untreated: 1.51 (0.21-10.98); p = 0.740 Treated: 1.12 (0.56-2.23); p = 0.680 1.04 (0.99-1.08) (Note: depression as a neuroticism measure)	Subsyndromal: 1.23 (0.50-3.02); p = 0.640 Non-severe depression: 0.81 (0.37-1.76); p = 0.590 Severe depression: <b>4.30 (1.39-13.33); p = 0.011</b> Depression at baseline and wave 2: 1.02 (0.47-2.21); p = 0.960 NR
Wilson 2011 (Rush Memory and Aging Project) (N = 785)	NEO Personality Inventory-Revised	HR (95% CI) for incident Alzheimer disease; mean 3.4-year follow-up <sup>a</sup>		
<b>Both dementia and Alzheimer disease</b>				
Brommelhoff 2009 (HARMONY, Swedish Twin Registry) (12,680)	Registry data and ICD codes	OR (95% CI) incident all-cause dementia; lifetime history assessed <sup>a</sup> OR (95% CI) incident Alzheimer disease; lifetime history assessed <sup>a</sup>	All depression: <b>1.72 (1.07-2.76); p &lt; 0.05</b> Recent onset: <b>3.87 (2.10-7.14); p &lt; 0.0001</b> Early onset: 0.90 (0.44-1.85) All depression: 1.20 (0.63-2.30) Recent onset: <b>2.62 (1.12-6.17); p &lt; 0.05</b> Early onset: 0.66 (0.24-1.81)	NR NR
Geerlings 2008 (Rotterdam Scan Study) (N = 486)	Participant history; CES-D ≥16	HR (95% CI) incident all-cause dementia; mean 5.9-year follow-up <sup>j</sup> OR (95% CI) incident Alzheimer disease; mean 5.9-year follow-up <sup>j</sup>	History of depression: <b>2.86 (1.45-5.63)</b> Early onset: <b>3.37 (1.39-8.17)</b> Late onset: <b>2.51 (1.08-5.85)</b> History of depression: <b>2.97 (1.33-6.61)</b> Early onset: <b>3.76 (1.41-10.06)</b> Late onset: 2.34 (0.82-6.69)	<u>CES-D</u> ≥16: 1.35 (0.55-3.30) Per point increase: 0.99 (0.94-1.03) <u>CES-D</u> ≥16 (presence of depressive symptoms): 1.36 (0.49-3.76) Per point increase: 0.99 (0.95-1.04)
Heser 2013 (AgeCoDe) (N = 2663)	DSM-IV MDD criteria assessed using CIDI-SF	HR (95% CI) for all-cause dementia; 4.5-year follow-up <sup>k</sup>	Any MDD: 0.92 (0.62-1.37) Age of onset (continuous): 1.02 (1.00-1.04); p < 0.10 <u>Age of onset</u> ≤59: 0.64 (0.35-1.18) ≥60: 1.39 (0.83-2.34) ≥65: 1.65 (0.96-2.82); p < 0.10 ≥70: <b>2.22 (1.30-3.80); p &lt; 0.01</b>	GDS-15 ≥6 (clinically relevant depression): 1.33 (0.95-1.86); p < 0.10 <u>GDS-15 ≥6 and age of onset</u> ≥70: 1.52 (0.70-3.32) ≥75: <b>4.41 (1.96-9.91); p &lt; 0.001</b>

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
			<p>≥75: <b>2.29 (1.18-4.46); p &lt; 0.05</b></p> <p>Any MDD: 0.79 (0.43-1.46)</p> <p>Age of onset (continuous): <b>1.05 (1.01-1.10); p &lt; 0.05</b></p> <p><u>Age of onset</u></p> <p>≤59: 0.35 (0.11-1.11); p &lt; 0.10</p> <p>≥60: 1.53 (0.75-3.12)</p> <p>≥65: 1.73 (0.81-3.70)</p> <p>≥70: <b>2.40 (1.12-5.13); p &lt; 0.05</b></p> <p>≥75: <b>3.13 (1.38-7.09); p &lt; 0.01</b></p>	<p>GDS-15 ≥6 (clinically relevant depression): 1.24 (0.78-1.97)</p> <p><u>GDS-15 ≥6 and age of onset</u></p> <p>≥70: 1.85 (0.76-4.48)</p> <p>≥75: <b>7.29 (2.98-17.80); p &lt; 0.001</b></p>
		HR (95% CI) for Alzheimer disease; 4.5-year follow-up <sup>k</sup>	<p>Any MDD: 1.07 (0.62-1.86)</p> <p>Age of onset (continuous): 1.00 (0.97-1.03)</p> <p><u>Age of onset</u></p> <p>≤59: 1.00 (0.49-2.03)</p> <p>≥60: 1.24 (0.54-2.80)</p> <p>≥65: 1.58 (0.70-3.59)</p> <p>≥70: 2.18 (0.96-4.95); p &lt; 0.10</p> <p>≥75 years: 1.19 (0.30-4.83)</p>	<p>GDS-15 ≥6 (clinically relevant depression): 1.15 (0.67-1.97)</p>
		HR (95% CI) for dementia of other etiology; 4.5-year follow-up <sup>k</sup>		
Katon 2015 (DCRS) (N = 2,454,532)	ICD codes	HR (95% CI) for all-cause dementia; 6-year follow-up <sup>l</sup>	<p>MDD alone: <b>1.68 (1.64-1.71)</b></p> <p>MDD and diabetes: <b>1.82 (1.76-1.89)</b></p> <p>Age &lt;65: <b>2.93 (2.71-3.16)</b></p> <p>Age ≥65: <b>1.78 (1.75-1.82)</b></p>	NR
		HR (95% CI) for Alzheimer disease; 6-year follow-up <sup>l</sup>	<p>MDD alone: <b>1.39 (1.35-1.44)</b></p> <p>MDD and diabetes: <b>1.46 (1.37-1.55)</b></p>	NR
		HR (95% CI) for vascular dementia; 6-year follow-up <sup>l</sup>	<p>MDD alone: <b>2.42 (2.29-2.55)</b></p> <p>MDD and diabetes: <b>3.56 (3.28-3.86)</b></p>	NR
Lenoir 2011 (3C Study) (N = 7989)	DSM-IV MDD criteria assessed using MINI	HR (95% CI) for all-cause dementia; 4-year follow-up <sup>m</sup>	<p>Lifetime treated depression: 1.1 (0.8-1.5)</p> <p>MDE: 1.1 (0.7-1.7)</p> <p>Past MDE: 1.2 (0.8-2.0)</p> <p>Current MDE: 0.7 (0.3-2.0)</p>	<p>Baseline high levels of depressive symptoms: <b>1.5 (1.2-2.2); p = 0.01</b></p>
		HR (95% CI) for Alzheimer disease; 4-year follow-up <sup>m</sup>	NR	<p>Baseline high levels of depressive symptoms: 1.0 (0.7-1.6)</p>

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Richard 2013 (WHICAP) (N = 1943)	10-item CES-D ≥4	HR (95% CI) for vascular dementia; 4-year follow-up <sup>m</sup>	NR	Baseline high levels of depressive symptoms: <b>4.8 (2.2-10.7)</b>
		HR (95% CI) for all-cause dementia; mean 5.4-year follow-up <sup>n</sup>	All: <b>1.8 (1.2-2.7)</b> MCI at baseline: 1.8 (0.9-3.5) Depression at baseline only: 1.6 (1.0-2.5)	Depression at baseline and follow-up: <b>1.9 (1.3-2.8)</b>
		HR (95% CI) for Alzheimer disease; mean 5.4-year follow-up <sup>n</sup>	All: <b>1.9 (1.2-2.9)</b> MCI at baseline: 1.7 (0.8-3.9)	NR
Saha 2016 (NCODE) (N = 290)	DSM-IV MDD criteria	HR (95% CI) for vascular dementia; mean 5.4-year follow-up <sup>n</sup>	All: 1.7 (0.5-5.6) MCI at baseline: 3.7 (0.8-17.2)	NR
		HR (95% CI) for incident non-Alzheimer dementia; mean 7.1-year follow-up <sup>o</sup>	<u>By depression factor</u> Appetite: <b>2.10 (1.19-3.69); p = 0.01</b> Sadness: 1.53 (0.87-2.69) Guilt: 0.76 (0.48-1.20) Sleep: 0.77 (0.46-1.27) Anxiety: 0.95 (0.59-1.53) <u>By age of depression onset</u> <60: <b>3.39 (1.75-6.57); p &lt; 0.001</b> ≥60: 0.33 (0.09-1.19); p = 0.09	Not significant based on severity (MADRS and HAM-D); data NR
		HR (95% CI) for incident Alzheimer disease; mean 7.1-year follow-up <sup>o</sup>	<u>By depression factor</u> Appetite: <b>1.69 (1.06-2.67); p = 0.004</b> Sadness: 1.41 (0.91-2.17) Guilt: 0.78 (0.52-1.18) Sleep: 0.80 (0.52-1.23) Anxiety: 0.84 (0.55-1.27) <u>By age of depression onset</u> <60: 0.60 (0.22-1.62); p = 0.31 ≥60: 1.71 (0.93-3.16); p = 0.09	Not significant based on severity (MADRS and HAM-D); data NR
<b>Meta-analyses</b>				
Diniz 2013 (N = 49,612)	Any predefined cutoff from a depression	Pooled HR, OR, risk effect (95% CI) for all-cause dementia in	Pooled HR: <b>1.8 (95% CI: 1.52-2.14); p &lt; 0.0001</b> Pooled OR: <b>1.96 (95% CI: 1.64-2.34); p &lt; 0.0001</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
	assessment scale	patients with late-life depression	Pooled risk effect: OR <b>1.85 (95% CI: 1.67-2.04); p &lt; 0.0001</b> Confounder-adjusted studies only: OR <b>1.59 (1.41-1.80); p &lt; 0.001</b>	
		Pooled HR, OR, risk effect (95% CI) for Alzheimer disease in patients with late-life depression	Pooled HR: <b>1.54 (1.23-1.93); p &lt; 0.0001</b> Pooled OR: <b>1.85 (1.45-2.37); p &lt; 0.0001</b> Pooled risk effect: OR <b>1.65 (1.42-1.92); p &lt; 0.0001</b> Confounder-adjusted studies only: OR <b>1.55 (1.29-1.87); p &lt; 0.001</b>	NR
		Pooled HR, OR, risk effect (95% CI) for vascular dementia in patients with late-life depression	Pooled HR: <b>2.64 (1.35-5.17); p &lt; 0.0001</b> Pooled OR: <b>2.53 (1.42-4.50); p &lt; 0.0001</b> Pooled risk effect: OR <b>2.52 (1.77-3.59); p &lt; 0.0001</b> Confounder-adjusted studies only: <b>2.02 (1.27-3.21); p = 0.003</b>	NR
Ownby 2006 (N = 102,172)	Presence of symptoms consistent with MDD	Pooled OR (95% CI) for Alzheimer disease corrected for publication bias	Case-control studies: <b>1.96 (1.68-2.30); p &lt; 0.001</b> Cohort studies: <b>1.90 (1.55-2.33; p &lt; 0.001</b> All combined: <b>1.98 (1.76-2.24); p &lt; 0.001</b>	NR
<b>Populations with underlying comorbidities – diabetes</b>				
Katon 2010 (Pathways Epidemiologic Study) (N = 3837)	PHQ-9 DSM-IV criteria for MDD	HR (95% CI) for incident dementia in patients with diabetes; approximate 5-year follow-up <sup>d</sup>	All: <b>2.69 (1.77-4.07)</b> Developed dementia within 2 years: <b>2.05 (1.19-3.53)</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, and years of education.

<sup>b</sup> Adjusted for age, sex, practice, year of case diagnosis of dementia, anxiety, cerebrovascular disease, diabetes, dyslipidemia, hypertension, hypotension, IHD, interaction between anxiety and depression.

<sup>c</sup> Adjusted for age, sex, educational level, and cardiovascular diseases (hypertension, angina, coronary or other heart diseases and stroke).

<sup>d</sup> Adjusted for age, sex, education level, ethnicity; diabetes duration, treatment intensity (insulin or no insulin treatment), expected costs (RxRisk), diabetes complications, hypertension (at baseline); BMI, smoking, HbA1c, physical inactivity, number of primary care visits per month.

<sup>e</sup> Adjusted for age, education, hypertension, and stroke.

<sup>f</sup> Adjusted for age, sex, education, marital status, functional and cognitive impairment.

<sup>g</sup> Models including MCI were adjusted for interaction  $\ln A\beta 42$  and GDS score, years of education, creatinine level, years of smoking, and presence of at least one APOE e4 allele; group excluding MCI adjusted for interaction  $\ln A\beta 42$  and GDS score, years of education, creatinine level, years of smoking, and stroke or cerebral infarction in MRI.

<sup>h</sup> Adjusted for age, baseline MMSE, amnesic subtype of MCI, presence of APOE e4 allele.

<sup>i</sup> Adjusted for age, sex, education level, MMSE at baseline and functional disability, vascular risk factors and diseases.

<sup>j</sup> Adjusted for age, sex, education level, general cognitive functioning, and subjective memory complaint score; additionally adjusted for total hippocampal and amygdalar volume on MRI for all analyses aside from risk per point increase on CES-D.

<sup>k</sup> Adjusted for covariates and depression parameters, cognition parameters, subjective memory impairment (analyses of depression severity only, unadjusted for depression prevalence).

<sup>l</sup> Adjusted for age, sex, calendar period, marital status, IHD, CHF, peripheral vascular disease, atrial fibrillation or flutter, cerebrovascular disease, traumatic brain injury, COPD, complications of diabetes (retinopathy, renal disease, and neuropathy).

<sup>m</sup> Adjusted for age, sex, education level and center, baseline score of MMSE, BMI, hypertension, hypercholesterolemia, history of cardiovascular event, psychotropic drugs intake, memory complaint, self-perceived health, functional limitations in Instrumental Activities of Daily Living, and APOE genotype.

<sup>n</sup> Adjusted for age, sex, and vascular risk factors.

<sup>o</sup> Adjusted for age, sex, education level, and ethnicity.

3C, Three City; AGE-CAT, Automated Geriatric Examination for Computer Assisted Taxonomy; AgeCoDe, German Study on Ageing, Cognition, and Dementia in Primary Care Patients; AMDP, association for methodology and documentation in psychiatry; APOE, apolipoprotein E; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CHF, congestive heart failure; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; CiPCA, Consultations in Primary Care Archive; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DCRS, Danish Civil Registration System; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Geriatric Depression Scale; GMS, Geriatric Mental State; HAM-D, Hamilton Depression Rating Scale; HbA1c, hemoglobin A1c; HR, hazard ratio; ICD, International Classification of Diseases; ICPC, International Classification of Primary Care; IHD, ischemic heart disease; LEILA, Leipzig Longitudinal Study of the Aged; MCI, mild cognitive impairment; MDD, major depressive disorder; MDE, major depressive episode; MedDRA, Medical Dictionary for Regulatory Activities; MINI, Mini International Neuropsychiatric Interview; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MRC, Medical Research Council; NACC, National Alzheimer's Coordinating Centre; NCODE, Neurocognitive Outcomes of Depression in the Elderly; NOS, not otherwise specified; NR, not reported; NS, not significant; OR, odds ratio; PHQ, Patient Health Questionnaire; SCID, Structured Clinical Interview for DSM-IV disorders; UDS, Uniform Dataset; VITA, Vienna Transdanube Aging; WHICAP, Washington Heights-Inwood Columbia Aging Project; ZARADEMP, Zaragoza Dementia and Depression.

## Parkinson disease

### *Association Between Depression and Risk of Incident Parkinson Disease*

One US-based case-control study, Fang 2010 (N = 280,950), and one meta-analysis, Wang 2018 (N = 475,615), evaluated the association between depression and Parkinson disease. Both showed a positive association between depression and incident Parkinson disease overall (OR 2.0; 95% CI: 1.6-2.4 for Fang 2010 and RR 2.20; 95% CI: 1.87-2.58 for Wang 2018) and across several subgroups (e.g. males and females, geographic location, study type, and method used for depression assessment). One of the few exceptions was a subgroup in the Fang 2010 study, which found that the association lost significance for patients who had a depression diagnosis between 1985 and 1994 (OR 1.3; 95% CI: 0.8-2.1; note that study data collection period was 1995-2006). An additional subgroup analysis of patients with depression diagnosed prior to 1995 and age <62 years at baseline also lost significance in the multivariate analysis (OR 1.4; 95% CI: 0.9-2.1), whereas those age ≥62 years did not (OR 1.8; 95% CI: 1.4-2.4). These findings suggest a potential temporal and age-mediated relationship between depression and the development of Parkinson disease, and both studies acknowledge that, as with dementia and Alzheimer disease, depression may be a prodromal symptom of Parkinson disease to a certain extent.

### *Association Between Depression and Parkinson Disease Severity*

No studies were identified by the review for this association.

## Epilepsy

### *Association Between Depression and Risk of Incident Epilepsy*

The impact of depression on incident epilepsy was assessed in 2 UK-based studies: Farmer 2008 (N = 2430), a case-control study, and Josephson 2017 (N = 2573), which used prospectively collected data from The Health Improvement Network (THIN) database. Whereas Farmer 2008 did not demonstrate a significant association between lifetime history of recurrent depression and the development of epilepsy (OR 3.06; 95% CI: 0.90-10.47), Josephson 2017 showed a strong association over a prospective 5-year follow-up across models adjusted for several covariates (for example, HR 2.54; 95% CI: 2.48-2.60;  $p < 0.001$  in a model adjusted for age, sex, Charlson Comorbidity Index, and Townsend Deprivation Index). Furthermore, the association remained significant in subgroup analyses in patients with treated depression (HR 3.45; 95% CI: 3.40-3.50;  $p < 0.001$ ), and in sensitivity analyses in those who used either antidepressant medications alone (HR 3.43; 95% CI: 3.37-3.47;  $p < 0.001$ ) or antidepressant medications and counselling (HR 9.85; 95% CI: 5.74-16.90;  $p < 0.001$ ). The Josephson 2017 study also assessed the opposite direction, finding evidence of a bi-directional relationship with incident depression in patients with epilepsy (HR 2.04; 95% CI: 1.97-2.09;  $p < 0.001$ ).

These 2 studies differ in certain ways: the THIN database [Josephson 2017] was comprised of a sample of over 10 million participants, identifying over 97,000 people who developed epilepsy from medical records, whereas the Farmer 2008 study was smaller with 1546 cases and 887 controls that relied on patient interview of lifetime history to identify diagnoses. Josephson 2017 also specifically assessed patients with single episodes of depression, whereas Farmer 2008 was restricted to a population with recurrent depression. Lastly, it should be noted that Farmer 2008 examines lifetime prevalence of comorbidities; it is unclear if these were determined to have occurred after MDD episodes.

#### *Association Between Depression and Epilepsy Severity*

Two studies were identified that assessed the impact of depression on epilepsy disease severity: Josephson 2017 (N = 2573) conducted a separate analysis from the UK THIN database that assessed 1-year seizure freedom rates in a Canadian database of people with epilepsy, and Patel 2018 (N = 397,440) assessed in-hospital mortality rates for those with a diagnosis of epilepsy in a hospitalization database in the US. Although no association was observed between depression and in-hospital mortality (data not reported) [Patel 2018], past or current depression did lead to higher odds of failing to achieve 1-year seizure freedom compared to those without depression (OR 1.41; 95% CI: 1.03-1.96; p = 0.03), and this relationship was not altered considerably when restricted to those who were undergoing depression treatment only [Josephson 2017].

## CVD

### General CVD

**Supplementary Table 11. Summary of studies assessing the association between depression and general CVD incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Almas 2015 (PART) (N = 10,341)	DSM-IV criteria assessed using MDI	OR (95% CI) for association between depression of varying severity and CVD; 10- to 13-year follow-up <sup>a,b</sup>	Overall depression: <b>1.5 (1.1-2.1)</b>	Mild depression: 1.3 (0.8-2.2) Moderate depression: <b>2.1 (1.3-3.5)</b> Severe depression: 1.3 (0.9-2.2)
Bremmer 2006 (N = 2403)	All patients with CES-D >16 diagnosed with the DSM-III MDD criteria assessed using DIS	RR (95% CI) of a cardiac event associated with baseline depression; mean 7.2-year follow-up with interviews every 3-years	<u>First non-ischemic cardiac event<sup>c</sup></u> MDD: 0.96 (0.24-3.89) <u>Any cardiac event<sup>d</sup></u> MDD: <b>2.09 (1.13-3.85)</b>	<u>First non-ischemic cardiac event<sup>c</sup></u> Subthreshold depression: 1.34 (0.82-2.18) <u>Any cardiac event<sup>d</sup></u> Subthreshold depression: 1.35 (0.96-1.90)
Case 2018 (NESARC) (N = 28,726)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for depression as a predictor of incident CVD; mean 36.6-month follow-up <sup>e</sup>	<u>Atypical depression</u> Non-atypical MDD: <b>1.28 (1.08-1.51); p &lt; 0.05</b> Atypical MDD: <b>1.56 (1.19-2.03); p &lt; 0.05</b> <u>Double depression</u> MDD: <b>1.26 (1.04-1.51); p &lt; 0.05</b> Double depression: <b>1.65 (1.46-1.87); p &lt; 0.05<sup>f</sup></b>	<u>Atypical depression</u> Dysthymic disorder only: 1.12 (0.82-1.54) <u>Double depression</u> Dysthymic disorder only: 1.12 (0.82-1.54)
Goldstein 2015 (NESARC) (N = 34,653)	Lifetime MDD assessed using AUDADIS-IV	OR (95% CI) for incidence of CVD; mean 39.96-month follow-up <sup>g</sup>	1.22 (0.99-1.51); p = 0.0585	NR
Graham 2019 (N = 134,860)	Participant interview (MDD if report ≥1	HR (95% CI) for risk of adverse cardiovascular	<u>MDD only</u> Overall: 0.75 (0.54-1.04); p = 0.08 Males: 1.12 (0.9-1.39); p = 0.3	NR



Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
	episode with a duration of $\geq 2$ weeks and physician consultation)	event; median 63-month follow-up <sup>h</sup>	Females: 0.68 (0.42-1.1); $p = 0.12$ <u>MDD as a time-varying variable</u> Overall: <b>1.01 (1.004-1.02); <math>p = 0.00303</math></b> Males: <b>1.47 (1.24-1.74); <math>p = 0.00000871</math></b> Females: <b>1.02 (1.004-1.03); <math>p = 0.00619</math></b> <u>Hypertension + MDD</u> Overall: <b>1.66 (1.45-1.9); <math>p = 7.48 \times 10^{-14}</math></b> Males: <b>1.47 (1.24-1.74); <math>p = 8.71 \times 10^{-6}</math></b> Females: <b>2.18 (1.82-2.92); <math>p = 4.76 \times 10^{-11}</math></b>	
Ivanovs 2018 (N = 1565)	PHQ-9 $\geq 10$ for current and MINI for lifetime depression	OR, current and lifetime depression associated with CVD; lifetime history assessed	Current depression in women: <b>2.01; <math>p = 0.004</math></b> Lifetime depression in men: <b>3.29; <math>p = 0.03</math></b>	NR
Niranjan 2012 (NESARC) (N = 9174)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for association between MDD subtype and any CVD; lifetime history assessed <sup>i</sup>	With vs. without atypical features: 1.11 (0.89-1.39)	NR
Seldenrijk 2015 (NESDA) (N = 2541)	Clinical interviews using CIDI	HR (95% CI) for the incidence of CVD; mean 5.5-year follow-up <sup>j</sup>	Current depression: <b>2.33 (1.36-4.00); <math>p = 0.002</math></b> Remitted depression: 1.48 (0.89-2.47); $p = 0.13$ MDD, single episode: 1.23 (0.62-2.43); $p = 0.55$ <b>2.46 (1.14-5.30)</b>	Per SD increase of IDS: <b>1.51 (1.25-1.83); <math>p &lt; 0.001</math></b> MDD, recurrent episodes: <b>1.85 (1.02-3.36); <math>p = 0.04</math></b> Dysthymia: 1.74 (0.92-3.26); $p = 0.09$
van Marwijk 2015 (N = 282)	GDS-15 $\geq 5$ and diagnostic interview using PRIME-MD; severity measured with MADRS	HR (95% CI) for the association of depression with cardiovascular events; mean 743-day follow-up <sup>k</sup>		NR
Windle 2013 (N = 557)	DSM-IV criteria assessed using CIDI	OR (95% CI) predicting CVD in middle-aged and	Single MDD: 0.74 (0.25-2.16)	Recurrent MDD: <b>3.59 (1.39-9.26); <math>p &lt; 0.01</math></b>

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
		older adult women; 5-year follow-up <sup>l</sup>		
<b>Meta-analyses</b>				
Correll 2017 N = 3,211,768	ICD codes or diagnoses according to DSM-III/IV/5 criteria	Pooled RR (95% CI) for risk of CVD in patients with MDD	Longitudinal studies: <b>1.72 (1.48-2.00)</b> ; <b>p &lt; 0.0001</b>	NR
Van der Kooy 2007 (N ≈ 80,000)	Depressive symptoms or disorders	Pooled RR (95% CI) for CVD in patients with depressive symptoms or disorders	All depression: <b>1.46 (1.37-2.08)</b> Males only: <b>1.47 (1.22-1.77)</b> Females only: <b>1.38 (1.22-1.55)</b> MDD only: <b>2.54 (2.07-3.10)</b> Depressive symptoms only: <b>1.39 (1.26-1.54)</b>	NR
<b>Populations with underlying comorbidities – diabetes</b>				
Lin 2010 (Pathways Epidemiologic Study) <sup>m</sup> (N = 3723)	PHQ-9	HR (95% CI) for macrovascular outcomes in patients with diabetes; 5-year follow-up <sup>n</sup>	Minor depression: 1.00 (0.79-1.27) MDD: 1.25 (1.00-1.54)	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, socioeconomic status, BMI, history of IHD, stroke, hypertension, diabetes, smoking, physical activity, and hazardous alcohol consumption.

<sup>b</sup> All participants from wave 1 (1998-2000) were followed-up in wave 3 (2010) for the occurrence of CVD. Data from the National Patient Register had their follow-up from 2008-2011.

<sup>c</sup> Adjusted for age and sex.

<sup>d</sup> Adjusted for age, sex, education, marital status, excessive drinking, smoking, BMI, abdominal obesity, hypertension, diabetes, cognitive impairment, and the use of SSRIs or tricyclic antidepressants.

<sup>e</sup> Adjusted for age, sex, ethnicity, education, hypertension, hypercholesterolemia, diabetes, tobacco use, BMI, and lifetime anxiety disorder.

<sup>f</sup> Defined as MDD and dysthymia.

<sup>g</sup> Adjusted for age, sex, race, cigarette smoking, hypertension, obesity, and alcohol and drug use disorders.

<sup>h</sup> Adjusted for history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, SBP, sedentary hours per day, physical activity, and psychotropic medication use.

<sup>i</sup> Adjusted for age, sex, ethnicity, education, household income, profession, marital status, access to health insurance, BMI, smoking status, alcohol use pattern, stimulant use, and cocaine use.

<sup>j</sup> Adjusted for age, sex, education, hypertension, diabetes mellitus, triglycerides, BMI, smoking, alcohol use, and physical activity.

<sup>k</sup> Adjusted for CVD medication.

<sup>l</sup> Adjusted for age, education, baseline CVD, BMI, alcohol use, cigarette use, lifetime anxiety disorder, and stressful events.

<sup>m</sup> These data are also presented in the metabolic section as complications of diabetes.

<sup>n</sup> Adjusted for age, sex, ethnicity, education, marital status, any prior microvascular/macrovascular event, diabetes duration, treatment intensity, expected costs, hypertension, BMI, smoking, limited physical activity, and HbA1c.

AUDADIS, Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; CIDI, Composite International Diagnostic Interview; CVD, cardiovascular disease; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Geriatric Depression Scale; HbA1c, hemoglobin A1c; HR, hazard ratio; ICD, International Classification of Diseases; IDS, Inventory of Depressive Symptomatology; IHD, ischemic heart disease; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, Major depressive disorder; MDI, Major Depression Inventory; MINI, Mini International Neuropsychiatric Interview; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NESDA, Netherlands Study of Depression and Anxiety; NR, not reported; OR, odds ratio; PART, Psykisk hälsa, Arbete och Relationer; PHQ, Patient Health Questionnaire; PRIME-MD, Primary Care Evaluation of Mental Disorders; RR, risk ratio; SBP, systolic blood pressure; SD, standard deviation; SSRI, selective serotonin reuptake inhibitors.

### Supplementary Table 12. Summary of studies assessing the association between depression and CVD mortality in patients with pre-existing CVD

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Connerney 2010 (N = 309)	Modified DIS interview to assess MDD; BDI ≥10 indicates depressive symptoms	HR (95% CI) for cardiac mortality post-CABG surgery; median 9.3-year follow-up <sup>a</sup>	Current MDD: <b>1.78 (1.04-3.04); p = 0.04</b> Any MDD: <b>1.78 (1.04-3.04); p = 0.04</b> History of depression only: 1.47 (0.73-2.96); p = 0.28 MDD new depression only (after surgery and no history): <b>2.12 (1.09-4.15); p = 0.03</b> MDD and history of depression: 1.72 (0.78-3.80); p = 0.18 BDI ≥10: 1.67 (0.99-2.79); p = 0.05	BDI (continuous): <b>1.05 (1.00-1.09); p = 0.03</b> BDI somatic (continuous): 1.07 (0.98-1.16); p = 0.12 BDI cognitive-affective (continuous): <b>1.10 (1.03-1.17); p = 0.007</b>
Dickens 2008 (N = 588)	SCAN interview used to validate HADS ≥17 to indicate depressive disorder	HR (95% CI) for predictors of time to cardiac death post-MI; mean 6.7-year follow-up	New onset depression: <b>2.33 (1.05-5.16); p = 0.04</b> Pre-MI depression: 0.31; p = 0.12	NR
Rollman 2012 (N = 471)	PHQ-2 and PHQ-9	HR (95% CI) for CVD mortality post-heart failure; 12-month follow-up <sup>b</sup>	Overall: <b>2.7 (1.1-6.6); p = 0.03</b> After exclusion of patients taking antidepressants at baseline: 2.5 (1.0-6.2); p = 0.05	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Saint Onge 2014 (National Health Interview Survey) (N = 11,369)	CIDI-SF	HR (95% CI) for CVD mortality; 7-year follow-up <sup>c</sup>	CVD at baseline: 1.91 (0.96-3.79); p ≤ 0.10	NR
van den Broek 2011 (Cardiovascular Health Study) (N = 4114)	CES-D ≥8 indicates clinically relevant depression	HR (95% CI) of CVD-related mortality in patients with heart failure at baseline; median 10.7-year follow-up <sup>d</sup>	Overall: <b>2.07 (1.31-3.27)</b> Adjusted for cardiac medications: <b>1.76 (1.08-2.88)<sup>e</sup></b> Depressed, high NT-proBNP: <b>6.02 (2.86-12.67)</b> Non-depressed, high NT-proBNP: <b>3.03 (1.46-6.26)</b> Depressed, low NT-proBNP: <b>2.32 (0.85-6.31)</b>	Per square root CES-D unit: <b>1.26 (1.01-1.56)<sup>f</sup></b>
Willey 2010 (NOMASS) (N = 340)	HAM-D	HR (95% CI) for post-stroke mortality; follow-up every 6 months for 2 years then annually for 5 years <sup>g</sup>	Vascular death: 1.52 (0.81-2.88) Nonvascular death: 0.78 (0.41-1.50)	NR
<b>Meta-analyses</b>				
Fan 2014 (N = 679)	Any dichotomous classification	Pooled HR (95% CI) post-heart failure CVD mortality	<b>2.19 (1.46-3.29)</b>	NR
Meijer 2011 (N = 16,889)	Validated depression rating scale or structured diagnostic interview	Pooled OR (95% CI) post-MI cardiac mortality	<b>2.71 (1.68-4.36); p &lt; 0.001</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences (p < 0.05) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels of depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, LVEF, and diabetes.

<sup>b</sup> Adjusted for age, sex, LVEF, NYHA class, presence of an anxiety disorder, diabetes, renal insufficiency, blood pressure, presence of anemia, hyponatremia, use of an ACE-I or an ARB medication, and use of coumadin.

<sup>c</sup> Adjusted for age, sex, ethnicity, foreign birth, marital status, education, employment status, logged family income, alcohol consumption, physical activity, and smoking.

<sup>d</sup> Adjusted for age, sex, ethnicity, SBP, cholesterol, diabetes mellitus status, BMI, smoking, reduced physical activity, coronary heart disease at baseline, reduced LVEF, and left ventricular hypertrophy.

<sup>e</sup> Cardiac medications include beta-blockers, ACE-I, and diuretics.

<sup>f</sup> Adjusted for age, sex, and ethnicity.

<sup>g</sup> Adjusted for age, ethnicity, completing a high school education, having <3 friends, being unmarried, having Medicaid or no insurance, stroke severity, physical activity, CAD, and diabetes.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BDI, Beck Depression Inventory; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; CVD, cardiovascular disease; DIS, Diagnostic Interview Schedule; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Depression Rating Scale; HR, hazard ratio; LVEF, left ventricular ejection fraction; MDD, Major depressive disorder; MI, myocardial infarction; NOMASS, Northern Manhattan Stroke Study; NR, not reported; NT-proBNP, amino terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PHQ, Patient Health Questionnaire; SCAN, Schedules for the Clinical Assessment of Neuropsychiatry; SBP, systolic blood pressure.

**Supplementary Table 13. Summary of studies assessing the association between depression and CVD mortality in population-based cohorts**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Atlantis 2012 (NHANES; NHEFS) (N = 6394)	GWB-D (low: 19-25, medium: 13-8, high: 0-12) at baseline; CES-D ≥16 at follow-up indicated "new depression"	HR (95% CI) for CVD mortality associated with depression; mean 16.2-year follow- up <sup>a</sup>	Single diagnosis of depression Baseline: 1.0 (0.6-1.5); p = 0.888 Follow-up: 1.3 (1.0-1.8); p = 0.064	Depression severity at baseline Medium: 1.0 (0.9-1.2); p = 0.877 High: 1.1 (0.9-1.4); p = 0.465 <u>At baseline and follow-up</u> Two diagnoses of depression: 1.5 (0.9-2.3); p = 0.116
Butnoriene 2015 (N = 1115)	MDE DSM-IV- TR criteria assessed using MINI	HR (95% CI) for the association between MDE and CVD mortality during the 10-year follow-up in women; lifetime MDE <sup>b</sup>	<b>1.86 (1.11-3.12); p = 0.019</b>	NR
Egede 2005 (NHANES; NHEFS) (N = 10,025)	CES-D ≥16 indicates MDD	HR (95% CI) for CHD mortality associated with diabetes and depression diagnoses in 1982; mean 8- year follow-up <sup>c</sup>	Depression only: 1.29 (0.96-1.74) Diabetes + depression: <b>2.43 (1.66-3.56)</b>	NR
Gasse 2014 (DCRS) (N = 4,545,327)	ICD codes	RR (95% CI) of IHD mortality; index period of 1995-2009 for IHD events <sup>d</sup>	<u>Women</u> Overall: <b>1.68 (1.58-1.78)</b> Age 15-59 years: <b>2.57 (1.90-3.46)</b> Age 60-74 years: <b>2.25 (1.96-2.59)</b> Age ≥75 years: <b>1.55 (1.45-1.66)</b> <u>Men</u> Overall: <b>1.60 (1.46-1.75)</b> Age 15-59 years: <b>2.21 (1.79-2.74)</b> Age 60-74 years: <b>1.39 (1.16-1.66)</b> Age ≥75 years: <b>1.56 (1.38-1.76)</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Mykletun 2007 (HUNT-2) (N = 61,349)	HADS >8 indicated an optimal balance between sensitivity and specificity for MDD according to DSM III-TR/IV and ICD codes	OR (95% CI) for CVD mortality; mean 4.4-year follow-up <sup>e</sup>	Case-level depression: <b>1.36 (1.12-1.64)</b> ; <b>p &lt; 0.05</b>	Function of scale score for depression: <b>1.23 (1.12-1.34)</b> ; <b>p &lt; 0.05</b>
Pan 2011b (Nurses' Health Study) (N = 78,282)	Self-report for MDD; MHI-5 ≤52 indicates severe depressive symptoms <sup>f</sup>	RR (95% CI) of CVD mortality according to diabetes and depression status; follow-up of every 2-years for 6 years <sup>g</sup>	Depression only: <b>1.37 (1.16-1.62)</b> Diabetes + depression: <b>2.72 (2.09-3.54)</b> <u>MHI-5 ≥52</u> Depression only: 1.19 (0.99-1.43) Diabetes + depression: <b>2.57 (1.92-3.45)</b> <u>Antidepressant medication use</u> Depression only: <b>1.38 (1.17-1.63)</b> Diabetes + depression: <b>2.95 (2.28-3.81)</b> <u>Self-report of diagnosed depression</u> Depression only: <b>1.30 (1.08-1.55)</b> Diabetes + depression: <b>2.41 (1.80-3.23)</b>	NR
Saint Onge 2014 (National Health Interview Survey) (N = 11,369)	CIDI-SF	HR (95% CI) for CVD mortality; 7-year follow-up <sup>h</sup>	Full population: <b>2.27 (1.40-3.66)</b> ; <b>p ≤ 0.001</b> No CVD at baseline: <b>2.73 (1.08-6.91)</b> ; <b>p ≤ 0.05</b>	NR
Surtees 2008a (EPIC-Norfolk) (N = 20,627)	DSM-IV MDD criteria assessed using HLEQ	HR (95% CI) for fatal stroke; median 8.5-year follow-up <sup>i</sup>	Overall: 0.45 (0.11-1.84) Men: NR Women: 0.51 (0.12-2.15)	<u>MHI-5 score per SD decrease in scores</u> Overall: <b>1.22 (1.02-1.46)</b> Men: <b>1.42 (1.08-1.87)</b> Women: 1.12 (0.88-1.41)
Surtees 2008b (EPIC-Norfolk) (N = 2414)	DSM-IV MDD criteria assessed using HLEQ	OR (95% CI) for association between fatal IHD and past-year MDD; lifetime and past year history assessed <sup>j</sup>	1.90 (0.83-4.37)	NR
Surtees 2008c (EPIC-Norfolk) (N = 19,649)	DSM-IV MDD criteria assessed using HLEQ	HR (95% CI) for association between IHD	Overall: <b>2.67 (1.54-4.64)</b> <sup>k</sup> Men: <b>3.07 (1.55-6.08)</b> <sup>k</sup> Women: 2.05 (0.80-5.29) <sup>k</sup>	<u>Number of MDD episodes</u> <sup>l</sup> ≥3 episodes: <b>1.98 (1.28-3.05)</b> 1-2 episodes: 0.94 (0.54-1.61)

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
		mortality and 12-month MDD; median 8.5-year follow-up	<u>First episode of depression<sup>l</sup></u> Age ≥40: 1.44 (0.93-2.21) Age <40: 1.04 (0.57-1.91) <u>Age (years)<sup>l</sup></u> 41-49: <b>13.50 (1.88-97.7)</b> 50-59: <b>3.96 (1.34-11.7)</b> 60-69: 1.24 (0.39-3.96) 70-80: <b>2.81 (1.52-5.20)</b> <u>Antidepressant medication use<sup>l</sup></u> No: <b>2.68 (1.61-4.47)</b> Yes: 1.92 (0.56-6.53)	<b>p trend = 0.03</b> <u>Average duration of MDD<sup>l</sup></u> ≥6 months: <b>1.73 (1.04-2.88)</b> <6 months: 1.18 (0.74-1.89)
<b>Meta-analyses</b>				
Charlson 2013 (N >35,000)	Diagnosis by a physician or non-physician according to DSM criteria or ICD codes	Pooled RR (95% CI) for risk of fatal IHD events	1.54 (0.85-2.80)	NR
Correll 2017 (N = 3,211,768)	ICD codes or diagnoses according to DSM-III/IV/5 criteria	Pooled RR (95% CI) for risk of CVD mortality in patients with MDD	Longitudinal studies: <b>1.63 (1.25-2.13); p &lt; 0.0001</b>	NR
Nicholson 2006 (N = 146,538)	Self-completed questionnaire, diagnostic interview, physician diagnosis, anti-depressant medication, or self-reported diagnosis	Pooled RR (95% CI) for incidence of fatal CHD and mortality from coronary diseases <sup>m</sup>	Fatal CHD in patients without existing CVD at baseline (etiological studies): <b>1.69 (1.34-2.14)</b> Cardiac/cardiovascular mortality in patients with CHD at baseline (prognostic studies): <b>2.29 (1.33-3.94)</b>	NR
Shi 2017 (N = 118,954)	Valid questionnaires, structured interview, or	Pooled HR (95% CI) for risk of sudden cardiac death	<b>1.62 (1.37-1.92); p &lt; 0.001</b>	NR



Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Van der Kooy 2007 (N ≈ 80,000)	history of depression Depressive symptoms or disorders	Pooled RR (95% CI) for fatal CVD outcomes only in patients with depressive symptoms or disorders	<b>1.55 (1.35-1.75)</b>	NR
van Dooren 2013 (N = 11,375)	Clinical diagnosis or self-report	Pooled HR (95% CI) for depression and CVD mortality	<b>1.39 (1.11-1.73); p &lt; 0.0001</b>	NR
Wei 2019 (N = 198,589)	Physician diagnosis, use of antidepressant or standardized depressive symptoms scale	Pooled RR (95% CI) for depression and CVD mortality	Overall: <b>1.31 (1.20-1.43)</b> Mean age ≥75 years: <b>1.40 (1.08-1.83)</b> Mean age <75 years: <b>1.28 (1.16-1.42)</b> Males: 1.64 (0.86-3.14) Females: <b>1.24 (1.14-1.35)</b> Late-onset depression only: <b>1.40 (1.01-1.94)</b> <u>Assessment of depression via</u> Diagnosis/interview: <b>2.10 (1.07-4.11)</b> Standardized scale: <b>1.29 (1.18-1.41)</b> Standardized scale, GDS only: <b>1.56 (1.10-2.22)</b> Standardized scale, CES-D only: <b>1.33 (1.17-1.51)</b>	NR
Wu 2016 (N = 323,709)	Clinical diagnosis or standardized psychometric tool	Pooled RR (95% CI) for risk of mortality due to CHD	<b>1.36 (1.14-1.63)</b>	NR
<b><i>Populations with underlying comorbidities – diabetes</i></b>				
Coleman 2013, Lin 2009 (Pathways Epidemiologic Study) (N = 4623)	PHQ-9	HR (95% CI) for CVD-related mortality; 10-year follow-up <sup>n</sup>	<u>MDD</u> 5 years: 1.25 (0.83-1.86) 10 years: 1.27 (0.90-1.78)	<u>Minor depression</u> 5 years: 1.20 (0.81-1.78) 10 years: 1.04 (0.71-1.51)

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, all other demographics, lifestyle factors, prevalent medical conditions, and incident medical conditions.

<sup>b</sup> Adjusted for age, smoking, alcohol consumption, and physical activity.

<sup>c</sup> Adjusted for age in 1982, sex, ethnicity, poverty:income ratio, education, marital status, smoking, physical activity, BMI, aspirin use, and comorbid conditions at baseline including cancer, hypertension, heart disease, and stroke.

<sup>d</sup> Adjusted for calendar year, age group, and Charlson Comorbidity Index score.

<sup>e</sup> Adjusted for age, sex, somatic symptoms/diagnoses, physical impairment, smoking/alcohol use, physical activity, educational level, socioeconomic status, BMI, diastolic blood pressure, and total cholesterol level.

<sup>f</sup> Depression was defined as having diagnosed depression, being treated with antidepressant medications, having severe depressive symptoms, or having any of these conditions.

<sup>g</sup> Adjusted for age, family history of diabetes and cancer, parental history of MI, current marital status, ethnicity, BMI, physical activity level, alcohol consumption, smoking status, current multivitamin use, estrogen hormone use, current aspirin use, and major comorbidities including hypertension, hypercholesterolemia, heart disease, stroke, and cancer.

<sup>h</sup> Adjusted for age, sex, ethnicity, foreign birth, marital status, education, employment status, logged family income, alcohol consumption, physical activity, smoking, and health behaviors.

<sup>i</sup> Adjusted for age, sex, cigarette smoking, SBP, total cholesterol, obesity, pre-existing MI, diabetes, social class, education, hypertension treatment, family history of stroke, and antidepressant medication use.

<sup>j</sup> Adjusted for age, sex, time of enrollment, cigarette smoking, diabetes, SBP, BMI, and cholesterol.

<sup>k</sup> Adjusted for age, sex, cigarette smoking, SBP, total cholesterol level, physical activity, BMI, diabetes, social class, heavy alcohol use, and antidepressant medication use.

<sup>l</sup> Adjusted for age and sex.

<sup>m</sup> Unadjusted.

<sup>n</sup> Adjusted for age, sex, ethnicity, education, and marital status, diabetes duration, treatment intensity, medical comorbidity (excluding diabetes, depression), hypertension diagnosis, BMI, smoking, limited physical activity, and glycosylated hemoglobin.

BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CHD, coronary heart failure; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; CVD, cardiovascular disease; DCRS, Danish Civil Registration System; DSM, Diagnostic and Statistical Manual of Mental Disorders; EPIC, European Prospective Investigation into Cancer; GDS, Geriatric Depression Scale; GWB-D, General Well-Being Schedule depression construct subscale; HADS, Hospital Anxiety and Depression Scale; HLEQ, Health and Life Experiences Questionnaire; HR, hazard ratio; HUNT, Health Study of Nord-Trøndelag County, Norway; ICD, International Classification of Diseases; IHD, ischemic heart disease; MDD, Major depressive disease; MDE, major depressive episode; MHI-5, Mental Health Inventory-5; MI, myocardial infarction; MINI, Mini International Neuropsychiatric Interview; NHANES, National Health and Nutrition Examination Survey; NHEFS, National Health Epidemiologic Follow-up Study; NR, not reported; OR, odds ratio; PHQ-9, Patient Health Questionnaire; RR, risk ratio; SBP, systolic blood pressure; SD, standard deviation.

## Heart failure

**Supplementary Table 14. Summary of studies assessing the association between depression and heart failure incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Empana 2006 (Group Health Cooperative) (N = 6392)	Medical records <sup>a</sup>	OR (95% CI) for out-of-hospital cardiac arrest associated with clinical depression; study period January 1, 1980-December 31, 1994 <sup>b</sup>	Overall (with and without pre-existing heart disease): <b>1.43 (1.18-1.73)</b> Without existing heart disease: <b>1.71 (1.22-2.41)</b> Excluding patients taking antidepressant medication: <b>1.37 (1.07-1.75)</b> Adjusted for antiarrhythmic agents: <b>1.43 (1.19-1.73)</b> Men: <b>1.47 (1.08-1.98)</b> Women: <b>1.40 (1.09-1.79)</b> Age <70 years: 1.21 (0.93-1.58) Age ≥70 years: <b>1.70 (1.29-2.23)</b>	Less severe clinical depression: <b>1.30 (1.04-1.63)<sup>c</sup></b> Severe clinical depression: <b>1.77 (1.28-2.45)<sup>d</sup></b> Trend: p < 0.001
van den Broek 2011 (Cardiovascular Health Study) (N = 4114)	CES-D ≥8 indicates clinically relevant depression	HR (95% CI) of incident heart failure; median 10.7-year follow-up <sup>e</sup>	Overall: 1.08 (0.92-1.26) Adjusted for cardiac medications: 1.13 (0.96-1.32) <sup>f</sup> Depressed, high NT-proBNP: <b>2.91 (2.32-3.65)</b> Non-depressed, high NT-proBNP: <b>2.81 (2.42-3.27)</b> Depressed, low NT-proBNP: <b>1.33 (1.07-1.64)</b>	Per square root CES-D unit: <b>1.09 (1.02-1.17)<sup>g</sup></b>
<b>Meta-analyses</b>				
Correll 2017 (N = 3,211,768)	ICD codes or diagnoses according to DSM-III/IV/5 criteria	Pooled RR (95% CI) for risk of CHF in patients with MDD	Longitudinal studies: <b>2.02 (1.48-2.75); p &lt; 0.0001</b>	NR
Shi 2017 (N = 118,954)	Valid questionnaires, structured interview, or history of depression	Pooled HR (95% CI) for risk of arrhythmias	Ventricular tachycardia/ventricular fibrillation: <b>1.47 (1.23-1.76); p &lt; 0.001</b> Atrial fibrillation (new-onset and recurrent): 1.43 (0.99-2.05); p = 0.056 New-onset atrial fibrillation: 0.96 (0.87-1.04); p = 0.311	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
			Recurrent atrial fibrillation: <b>1.88 (1.54-2.30)</b> ; <b>p &lt; 0.001</b>	
<b>Populations with underlying comorbidities</b>				
Davis 2008 (N ≈ 600,000)	Medical claims data <sup>h</sup>	RR (95% CI) for transitions between health states and CVD progression according to time frame of depression diagnosis; followed-up in 1-year intervals every quarter for 6 years <sup>i</sup>	<u>Past year</u> Hypertension + dyslipidemia → hypertension + dyslipidemia + CHF: <b>2.6 (2.1-3.3)</b> Hypertension + dyslipidemia + diabetes → hypertension + dyslipidemia + diabetes + CHF: <b>2.2 (1.7-2.8)</b> <u>Past 1-2 years</u> Hypertension + dyslipidemia → hypertension + dyslipidemia + CHF: <b>2.5 (1.8-3.3)</b> Hypertension + dyslipidemia + diabetes → hypertension + dyslipidemia + diabetes + CHF: <b>2.1 (1.5-3.0)</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Patients with clinical physician-diagnosed depression (referred to as clinical depression) were included if a physician reported the diagnosis of depression in the medical record within the year of the index date or if the enrollee was being treated with antidepressant medication at the index date based on the automated pharmacy data.

<sup>b</sup> Adjusted for current cigarette smoking, heavy alcohol consumption, physician-diagnosed diabetes mellitus, hypertension, prior MI, and prior CHF.

<sup>c</sup> Defined as no mental health clinic or hospitalization.

<sup>d</sup> Defined as a referral to mental health clinic and/or hospitalization for depression.

<sup>e</sup> Adjusted for age, sex, ethnicity, SBP, cholesterol, diabetes mellitus status, BMI, smoking, reduced physical activity, CHD at baseline, reduced LVEF, and left ventricular hypertrophy.

<sup>f</sup> Cardiac medications include beta-blockers, ACE-I, and diuretics.

<sup>g</sup> Adjusted for age, sex, ethnicity, and elevated NT-pro-BNP only.

<sup>h</sup> Using claims activity during a year, a patient was categorized as having MDD if he/she had 1 diagnosis of MDD in an inpatient setting or 2 diagnoses in an outpatient setting. MDD was not considered to be persistent.

<sup>i</sup> Adjusted for age and sex.

ACE-I, Angiotensin-converting enzyme inhibitor; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, hazard ratio; ICD, International Classification of Diseases; LVEF, left ventricular ejection fraction; MDD, Major depressive disorder; MI, myocardial infarction; NR, not reported; NT-proBNP, amino terminal pro-B-type natriuretic peptide; OR, odds ratio; RR, risk ratio; SBP, systolic blood pressure.

**Supplementary Table 15. Summary of studies assessing the association between depression and heart failure severity or mortality**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Empana 2006 (Group Health Cooperative) (N = 6392)	Medical records <sup>a</sup>	OR (95% CI) for out-of-hospital cardiac arrest; study period January 1, 1980-December 31, 1994 <sup>b</sup>	Overall (with and without pre-existing heart disease): <b>1.43 (1.18-1.73)</b> Patients with existing heart disease: <b>1.27 (1.01-1.60)</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Patients with clinical physician-diagnosed depression (referred to as clinical depression) were included if a physician reported the diagnosis of depression in the medical record within the year of the index date or if the enrollee was being treated with antidepressant medication at the index date based on the automated pharmacy data.

<sup>b</sup> Adjusted for current cigarette smoking, heavy alcohol consumption, physician-diagnosed diabetes mellitus, hypertension, prior MI, and prior CHF. CI, confidence interval; CHF, congestive heart failure; MI, myocardial infarction; NR, not reported; OR, odds ratio.

## Hypertension

**Supplementary Table 16. Summary of studies assessing the association between depression and hypertension incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
<i>Hypertension only</i>				
Davis 2008 (N ≈ 600,000)	Medical claims data <sup>a</sup>	RR (95% CI) for transitions between health states and CVD progression according to time frame of depression diagnosis; followed-up in 1-year intervals every quarter for 6 years <sup>b</sup>	<u>Past year</u> Healthy → hypertension: <b>1.4 (1.3-1.4)</b> Dyslipidemia → dyslipidemia + hypertension: <b>1.6 (1.5-1.7)</b> <u>Past 1-2 years</u> Healthy → hypertension: <b>1.8 (1.7-1.9)</b> Dyslipidemia → dyslipidemia + hypertension: <b>1.5 (1.4-1.6)</b>	NR
Farmer 2008 (N = 2430)	Interviews using SCAN version 2.1; DSM-IV-TR or ICD codes used to assess recurrence	OR (95% CI) for hypertension in patients with recurrent depression; lifetime history assessed	NR	Recurrent: <b>2.20 (1.51-3.22); p = 0.00062<sup>c</sup></b>
Niranjan 2012 (NESARC) (N = 9174)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for association between MDD and hypertension; lifetime history assessed	MDD vs. no MDD: <b>1.26 (1.14-1.40); p &lt; 0.0001<sup>d</sup></b> MDD with atypical features vs. without: 1.16 (0.90-1.49) <sup>e</sup>	NR
Patten 2008, Patten 2009a (NPHS) (N = 15,254)	DSM-IV MDD criteria assessed using CIDI-SF	HR (95% CI) for incidence of hypertension; 8- and 10- year study period with assessments every 2-years <sup>f</sup>	<u>MDD at baseline interview</u> 8 years: <b>1.6 (1.2-2.2)</b> 10 years: <b>1.6 (1.2-2.2); p = 0.002</b> <u>MDD as a time-varying characteristic</u> 8 years: 1.3 (1.0-1.7) 10 years: 1.3 (0.9-1.9)	<u>By duration of past-year MDD episode<sup>g</sup></u> 2-12 weeks: 1.0 (0.7-1.4) 13-52+ weeks: <b>2.0 (1.2-3.3)</b>

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Zambrana 2016 (Women's Health Initiative) (N = 4680)	CES-D and DIS	OR (95% CI) for incident prehypertension and hypertension in women who were normotensive at baseline; 3-year follow-up	<u>Baseline depression<sup>h</sup></u> Prehypertension: 0.83 (0.58-1.18) Hypertension: 1.53 (0.95-2.46) <u>History of depression<sup>i</sup></u> Prehypertension: <b>1.27 (1.01-1.61)</b> Hypertension: 1.08 (0.84-1.39)	NR
<b><i>Hypertension as part of metabolic syndrome</i></b>				
Block 2016 (SHIP-0; SHIP-TREND-0) (N = 8040)	DSM-IV MDD criteria assessed using CID-S and M-CIDI	OR (95% CI) for association between MDD and hypertension; lifetime history assessed <sup>j</sup>	<u>Females</u> SHIP-0, depression at syndromal level: 0.95 (0.73-1.24) SHIP-TREND-0, depression at syndromal level: 0.98 (0.78-1.22) MDD lifetime: 0.99 (0.77-1.28) <u>Males</u> SHIP-0, depression at syndromal level: 1.01 (0.70-1.45) SHIP-TREND-0, depression at syndromal level: 1.04 (0.81-1.35) MDD lifetime: 1.33 (0.99-1.78)	<u>Recurrent MDD</u> Females: 1.24 (0.93-1.65) Males: 1.24 (0.87-1.78)
Goldbacher 2009 (SWAN) (N = 429)	DSM-IV MDD criteria assessed using SCID-IV	HR (95% CI) for depression as a predictor of hypertension; 7-year follow-up	1.18 (0.80-2.16)	NR
<b><i>Meta-analysis</i></b>				
Meng 2012 (N = 22,367)	Self-reports or interviews	Pooled RR (95% CI) for incident hypertension	Overall: <b>1.42 (1.09-1.86); p = 0.009</b> Studies reporting unadjusted results: 1.12 (0.85-1.48) Studies reporting adjusted results: 1.38 (0.91-2.09) <9.6 years follow-up: 1.02 (0.98-1.06) >9.6 years follow-up: <b>1.57 (1.06-2.34)</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported

where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Using claims activity during a year, a patient was categorized as having MDD if he/she had 1 diagnosis of MDD in an inpatient setting or 2 diagnoses in an outpatient setting. MDD was not considered to be persistent.

<sup>b</sup> Adjusted for age and sex.

<sup>c</sup> p-value corrected for multiple testing.

<sup>d</sup> Adjusted for age, sex, ethnicity, education, family income, and health insurance.

<sup>e</sup> Adjusted for age, sex, ethnicity, education, household income, profession, marital status, access to health insurance, BMI, smoking status, alcohol use pattern, stimulant use, and cocaine use.

<sup>f</sup> Adjusted for age, sex, and  $\geq 2$  physician visits during preceding year (8-year analysis); Adjusted for age, sex, family history (first-degree relative) of high blood pressure, obesity, sedentary lifestyle, excessive consumption of alcohol, self-reported professionally diagnosed diabetes, current smoking status, Black ethnic status,  $\geq 1$  reported sources of stress from a list of chronic life stressors, exposure to antidepressant medications and other psychotropic medications, and diet that was low in fruit and vegetable consumption (10-year analysis).

<sup>g</sup> Unadjusted; 8-year data only.

<sup>h</sup> Adjusted for age, education, insurance, BMI, family history of diabetes, stroke, or MI, high cholesterol requiring pills, treated diabetes, history of CVD, smoking status, total energy expenditure/week, and alcohol intake.

<sup>i</sup> Adjusted for age, education, insurance, BMI, family history of diabetes, stroke, or MI, high cholesterol requiring pills, treated diabetes, history of CVD, smoking status, total energy expenditure/week, alcohol intake, antidepressant use, caregiving, stressful life events, social support, and optimism.

<sup>j</sup> Adjusted for age categories, education, marital status, employee status, smoking, physical inactivity, and risky alcohol consumption.

AUDADIS, Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; CID-S, Composite International Diagnostic-Screener; CVD, cardiovascular disease; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, hazard ratio; ICD, International Classification of Diseases; M-CIDI, Munich-Composite International Diagnostic Interview; MDD, Major depressive disorder; MI, myocardial infarction; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NPHS, National Population Health Survey; NR, not reported; OR, odds ratio; RR, risk ratio; SCAN, Schedules for the Clinical Assessment of Neuropsychiatry; SCID, Structured Clinical Interview for DSM-IV disorders; SHIP, Study of Health In Pomerania; SWAN, Study of Women's Health Across the Nation.

### *Association Between Depression and Hypertension Severity*

The Hiles 2016 study (N = 2776) assessed the impact of depression on individual components of metabolic syndrome, including hypertension (systolic blood pressure [SBP]  $\geq 130$  mmHg). Antidepressant use and severity of depression (measured by Inventory of Depressive Symptomatology [IDS] score) at year 0 and year 2 were not significantly associated with disease worsening (increases in SBP) in years 2 and 6, respectively ( $\beta \pm SE = 0.4676 \pm 0.6468$ ;  $p = 0.470$  and  $-0.2191 \pm 0.7495$ ;  $p = 0.770$ , respectively, for antidepressant use;  $\beta \pm SE = -0.0121 \pm 0.0189$ ;  $p = 0.523$  and  $0.0024 \pm 0.0267$ ;  $p = 0.928$ , respectively, for IDS score). Additionally, there were no significant findings in the bi-directional relationship, i.e. high SBP was not associated with subsequent changes in depression severity or antidepressant use at next assessment (year 0 to 2 or year 2 to 6).



IHD/CAD/CHD

**Supplementary Table 17. Summary of studies assessing the association between depression and IHD/CAD/CHD incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Almas 2015 (PART) (N = 10,341)	DSM-IV criteria assessed using MDI	OR (95% CI) for association between depression of varying severity and IHD; 10- to 13-year follow-up <sup>a,b</sup>	Overall depression: 1.5 (1.0-2.1)	Mild depression: 1.7 (1.0-3.0) Moderate depression: 1.7 (0.9-3.3) Severe depression: 1.1 (0.6-2.0)
Bremmer 2006 (N = 2403)	All patients with CES-D >16 diagnosed with the DSM-III MDD criteria assessed using DIS	RR (95% CI) of a first ischemic event associated with baseline depression; mean 7.2-year follow-up with interviews every 3-years <sup>c</sup>	MDD: <b>3.00 (1.51-5.93)</b>	Subthreshold depression: 1.37 (0.86-2.18)
Brunner 2014 (Whitehall II) (N =10,297)	Caseness defined as a score of ≥5 on GHQ-30 or ≥16 on CES-D	HR (95% CI) for incidence of major CHD; patients assessed clinically every ~6 years with total 24-year follow-up <sup>d</sup>	<u>Over 5 years (no lag)</u> Incident event: 1.17 (0.93-1.46); p = 0.18 Single episode: 1.00 (0.77-1.29) <u>Over 10 years (5-year lag)</u> Incident event: 1.22 (0.98-1.53); p = 0.08 Single episode: 1.31 (0.98-1.74) <u>Phase 7 (~18-year) analysis</u> CES-D caseness: <b>1.81 (1.07-3.06); p = 0.03</b>	<u>Over 5 years (no lag)</u> Incident event: 1.17 (0.90-1.46); p = 0.18 Multiple episodes: <b>1.47 (1.13-1.91); p trend = 0.01</b> <u>Over 10 years (5-year lag)</u> Incident event: 1.22 (0.98-1.53); p = 0.08 Multiple episodes: <b>1.43 (1.04-1.96); p trend = 0.02</b> <u>Phase 7 (~18-year) analysis</u> Cumulative GHQ caseness 1-2 times: 1.12 (0.72-1.74) Cumulative GHQ caseness 3-4 times: <b>2.06 (1.15-3.69); p trend = 0.04</b>
Gasse 2014 (DCRS) (N = 4,545,327)	ICD codes	IRR (95% CI) of IHD hospital admissions; index period of 1995-	<u>Women</u> Overall: <b>1.15 (1.10-1.20)</b> Age 15-59 years: <b>1.64 (1.50-1.78)</b> Age 60-74 years: <b>1.26 (1.18-1.35)</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
		2009 for IHD events <sup>e</sup>	Age ≥75 years: 0.87 (0.81-0.93) <u>Men</u> Overall: <b>1.14 (1.09-1.20)</b> Age 15-59 years: <b>1.39 (1.28-1.50)</b> Age 60-74 years: <b>1.10 (1.02-1.18)</b> Age ≥75 years: 0.90 (0.80-1.00)	
Herbst 2007 (NESARC) (N = 10,573)	DSM-IV MDE criteria assessed using AUDADIS-IV	OR (95% CI) for association between MDD and CHD; lifetime history assessed <sup>f</sup>	Lifetime MDD: <b>2.05 (1.70-2.48); p &lt; 0.05</b> Past-year MDD: <b>2.49 (1.81-3.43); p &lt; 0.05</b> 1 lifetime depressive episode: <b>2.10 (1.70-2.60)</b>	>1 depressive episode: <b>2.26 (1.75-2.91)</b> >1 vs. 1 episode: 1.07 (0.78-1.48)
Janszky 2010 (N = 49,321)	ICD codes	HR (95% CI) for risk of CHD; mean 37-year follow-up <sup>g</sup>	1.18 (0.80-1.75)	NR
Kendler 2009 (SALT; Swedish Twin Registry) (N = 30,374)	CIDI-SF	HR (95% CI) for prediction or future risk of CAD by MDD status or severity; data collected March 1998-January 2003	MDD and CAD in same year: <b>2.53 (1.70-3.78); p &lt; 0.001<sup>h</sup></b> MDD and CAD in subsequent years: <b>1.17 (1.04-1.31); p = 0.008<sup>h</sup></b> Single depressive episode: 1.03 (0.85-1.24); p = 0.79 <sup>h</sup>	<u>CIDI-SF met<sup>i</sup></u> 4 criteria: 0.46 (0.07-3.27); p = 0.11 5 criteria: 1.22 (0.99-1.51); p < 0.06 ≥6 criteria: <b>1.33 (1.15-1.54); p &lt; 0.001</b> Recurrent episodes: <b>1.32 (1.08-1.60); p = 0.007</b>
Ladwig 2006 (MONICA–KORA Augsburg) (N = 6239)	DEEX scale from the von Zerssen symptom checklist	HR (95% CI) for the prediction of future coronary events; mean 7.1-year follow-up <sup>j</sup>	Overall obesity x depression interaction: 1.73 (0.98-3.05); p = 0.060 <u>Men</u> Non-obese, depressed mood: 1.26 (0.88-1.80); p = 0.209 Obese, depressed mood: <b>2.32 (1.45-3.72); p &lt; 0.0001</b> <u>Women</u> Non-obese, depressed mood: 0.76 (0.35-1.69); p = 0.506 Obese, depressed mood: 1.84 (0.79-4.26); p = 0.158	NR
Liu 2017 (Americans <sup>k</sup> )	DSM-IV MDD criteria assessed using	OR (95% CI) of MDD as a	1.26 (0.67-2.37)	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Changing Lives study) (N = 1642)	diagnostic interview	predictor of CHD; 13-year follow-up <sup>k</sup>		
Mittag 2012 (Medicare Health Outcome Survey) (N = 37,290)	Participant interview	OR (95% CI) for association between depression and IHD; 2-year follow-up <sup>l</sup>	<b>1.53 (1.34-1.74)</b>	NR
Nabi 2010 (HeSSup) (N = 23,282)	BDI score of ≥10 defined threshold for subclinical mild to severe depression	HR (95% CI) for incident CHD events; 7-year follow-up <sup>m</sup>	Depressed (BDI ≥10): <b>1.47 (1.08-1.99); p &lt; 0.01</b> Antidepressant use: <b>1.72 (1.06-2.77); p &lt; 0.05</b>	Continuous BDI per 1-unit score increase: <b>1.03 (1.02-1.05); p &lt; 0.001</b> Mild depressive symptoms: <b>1.45; p = 0.0325</b> Moderate depressive symptoms: 1.58; p = 0.097 Severe depressive symptoms: 2.15; p = 0.784
Patten 2008 (NPHS) (N = 15,254)	CIDI-SF	HR (95% CI) for incidence of heart disease; 8-year study period with assessments every 2-years <sup>n</sup>	MDD at baseline interview: 1.4 (1.0–2.1) MDD as a time-varying characteristic: 1.2 (0.8-1.8)	<u>By duration of past-year MDD episode</u> <sup>o</sup> 2-12 weeks: 1.0 (0.5-2.0) 13-52+ weeks: 1.6 (0.9-3.1)
Surtees 2008b (EPIC-Norfolk) (N = 2414)	DSM-IV MDD criteria assessed using HLEQ	OR (95% CI) for fatal and nonfatal IHD; lifetime and past year history assessed	<u>Fatal and nonfatal IHD combined</u> <sup>p</sup> Overall: <b>1.55 (1.01-2.37)</b> Men: 1.36 (0.76-2.43) Women: 1.65 (0.88-3.12) <u>Nonfatal IHD</u> <sup>q</sup> Overall: <b>1.61 (1.01-2.57)</b>	NR
Wium-Andersen 2019 (N = 99,368)	ICD codes and MDI ≥25	HR (95% CI) for subsequent IHD; median 20.6-year follow-up	<u>Pooled cohort</u> <sup>r</sup> Overall: <b>1.63 (1.36-1.95); p &lt; 0.001</b> <u>Metropolit cohort</u> <sup>s</sup> Overall: <b>2.24 (1.49-3.48)</b> Hospital diagnosis with depression: 1.43 (0.74-2.78) Self-reported depression: <b>1.48 (1.17-1.87)</b> MDI score ≥25: <b>1.58 (1.03-2.42)</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
<b>Meta-analyses</b>				
Charlson 2013 (N >35,000)	Diagnosis by a physician or non-physician according to DSM criteria or ICD codes	Pooled RR (95% CI) for risk of incident IHD	Overall random effects: <b>1.56 (1.30-1.87)</b> Overall quality effects: <b>1.54 (1.27-1.87)</b> Non-fatal IHD events only: <b>1.8 (1.34-2.65)</b> Fatal and non-fatal IHD events: <b>1.51 (1.19-1.90)</b> Clinical diagnosis of depression: <b>2.50 (1.73-3.60)</b> Non-clinical diagnosis of depression: <b>1.40 (1.17-1.68)</b>	NR
Correll 2017 (N = 3,211,768)	ICD codes or diagnoses according to DSM-III/IV/5 criteria	Pooled RR (95% CI) for risk of CHD in patients with MDD	Longitudinal studies: <b>1.63 (1.33-2.00); p &lt; 0.0001</b>	NR
Leung 2012 (N = 127,590)	Valid questionnaire, structured interview, self-reports or medical records	Pooled RR (95% CI) of depression preceding CHD	Pre-morbid depression onset: <b>1.52 (1.25-1.84)<sup>†</sup></b> Non-incident depression: <b>1.59 (1.08-2.34)<sup>u</sup></b>	NR
Nicholson 2006 (N = 146,538)	Self-completed questionnaire, diagnostic interview, physician diagnosis, anti-depressant medication, or self-reported diagnosis	Pooled RR (95% CI) for incidence of new CHD events	Overall: <b>1.81 (1.53-2.15)<sup>o</sup></b> Depression measured with depressive symptom scale: <b>1.68 (1.38-2.04)<sup>o</sup></b> Depression measured with clinical diagnosis: <b>2.32 (1.76-3.06)<sup>o</sup></b>	NR
Van der Kooy 2007 (N ≈ 80,000)	Depressive symptoms or disorders	Pooled RR (95% CI) for CHD in patients with depressive symptoms or disorders	<b>1.48 (1.29-1.69)</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Wu 2016 (N = 323,709)	Clinical diagnosis or standardized psychometric tool	Pooled HR (95% CI) of MI and death due to CHD	Overall: <b>1.22 (1.13-1.32)</b> Restricted to studies excluding baseline CHD: <b>1.20 (1.11-1.30)</b> Baseline mean age <65 years: <b>1.30 (1.09-1.55)</b> Baseline mean age ≥65 years: <b>1.26 (1.10-1.44)</b> Men: <b>1.20 (1.06-1.36)</b> Women: 1.07 (0.99-1.17) Controlling for antidepressant use: <b>1.65 (1.19-2.30)</b> Not controlling for antidepressant use: <b>1.17 (1.08-1.26)</b>	NR
<b><i>Populations with underlying comorbidities</i></b>				
Davis 2008 (N ≈ 600,000)	Medical claims data <sup>v</sup>	RR (95% CI) for transitions between health states and CVD progression according to time frame of depression diagnosis; followed-up in 1-year intervals every quarter for 6 years <sup>w</sup>	<u>Past year</u> Hypertension → hypertension + CAD: <b>1.9 (1.5-2.4)</b> Dyslipidemia → dyslipidemia + CAD: <b>1.9 (1.5-2.3)</b> Hypertension + dyslipidemia → hypertension + dyslipidemia + CAD: <b>1.8 (1.6-2.1)</b> Hypertension + dyslipidemia + diabetes → hypertension + dyslipidemia + diabetes + CAD: <b>2.2 (1.9-2.6)</b> <u>Past 1-2 years</u> Hypertension → hypertension + CAD: <b>1.9 (1.4-2.5)</b> Dyslipidemia → dyslipidemia + CAD: <b>1.5 (1.1-2.1)</b> Hypertension + dyslipidemia → hypertension + dyslipidemia + CAD: <b>1.7 (1.4-2.1)</b> Hypertension + dyslipidemia + diabetes → hypertension + dyslipidemia + diabetes + CAD: <b>2.1 (1.7-2.6)</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported

where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, socioeconomic status, BMI, history of IHD, stroke, hypertension, diabetes, smoking, physical activity, and hazardous alcohol consumption.

<sup>b</sup> All participants from wave 1 (1998-2000) were followed-up in wave 3 (2010) for the occurrence of CVD. Data from the National Patient Register had their follow-up from 2008-2011.

<sup>c</sup> Adjusted for age, sex, education, marital status, excessive drinking, smoking, BMI, abdominal obesity, hypertension, diabetes, cognitive impairment, and the use of SSRIs or tricyclic antidepressants.

<sup>d</sup> Adjusted for age, sex, and ethnicity.

<sup>e</sup> Adjusted for calendar year, age group, and Charlson Comorbidity Index score.

<sup>f</sup> Multivariate analyses controlled for demographic characteristics, health variables, and substance use disorders.

<sup>g</sup> Adjusted for smoking, body length, diabetes, SBP, alcohol consumption, physical activity, father's occupation, family history of CHD, and geographic area.

<sup>h</sup> Adjusted for birth cohort, zygosity, and weighted index of genetic risk for MDD and CAD.

<sup>i</sup> Adjusted for zygosity, sex effects, birth cohort, and risk in year of onset.

<sup>j</sup> Adjusted for age, survey, total cholesterol, cigarette smoking, SBP, education, alcohol consumption, and physical activity.

<sup>k</sup> Adjusted for age, sex, BMI, wave 2 CHD, hypertension, diabetes, years of education, and interaction of MDD x functional social support.

<sup>l</sup> Adjusted for age, sex, hypertension, diabetes, and smoking history.

<sup>m</sup> Adjusted for age, sex, education, alcohol consumption, sedentary lifestyle, smoking, obesity, hypertension or diabetes, and incident CHD or incident cerebrovascular disease.

<sup>n</sup> Adjusted for age, sex, and  $\geq 2$  physician visits during preceding year.

<sup>o</sup> Unadjusted.

<sup>p</sup> Adjusted for age, sex, time of enrollment, cigarette smoking, diabetes, SBP, BMI, cholesterol, and C-reactive protein.

<sup>q</sup> Adjusted for age, sex, time of enrollment, cigarette smoking, diabetes, SBP, BMI, and cholesterol.

<sup>r</sup> Adjusted for age, sex, cohort, calendar year, education, marital status, alcohol use, smoking status, physical activity, BMI, SBP, total cholesterol, statin use, and stroke or IHD.

<sup>s</sup> Adjusted for education, daily alcohol use, smoke status, physical activity, and BMI.

<sup>t</sup> Data reported for pooled baseline CHD [worsening] and no CHD [incidence] groups.

<sup>u</sup> Data reported for baseline CHD group only (i.e. depression had previously occurred prior to CHD).

<sup>e</sup> Using claims activity during a year, a patient was categorized as having MDD if he/she had 1 diagnosis of MDD in an inpatient setting or 2 diagnoses in an outpatient setting. MDD was not considered to be persistent.

<sup>f</sup> Adjusted for age and sex.

AUDADIS, Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule; BDI, Beck Depression Inventory; BMI, body mass index; CAD, coronary artery disease; CES-D, Center for Epidemiological Studies-Depression; CHD, coronary heart disease; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; CVD, cardiovascular disease; DCRS, Danish Civil Registration System; DEEX, DEpression and EXhaustion subscale; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; EPIC, European Prospective Investigation into Cancer; GHQ, General Health Questionnaire; HeSSup, Health and Social Support; HLEQ, Health and Life Experiences Questionnaire; HR, hazard ratio; ICD, International Classification of Diseases; IHD, ischemic heart disease; IRR, incident rate ratio; KORA, Cooperative Health Research in the Region of Augsburg; MDD, Major depressive disorder; MDE, Major depressive episode; MDI, Major Depression Inventory; MI, myocardial infarction; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NPHS, National Population Health Survey; NR, not reported; OR, odds ratio; PART, Psykisk hälsa, Arbete och Relationer; RR, risk ratio; SALT, Screening Across the Lifespan Twin; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor.

**Supplementary Table 18. Summary of studies assessing the association between depression and post-IHD/CAD/CHD events**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Gasse 2014 (DCRS) (N = 4,545,327)	ICD codes	IRR (95% CI) of post-IHD cardiac interventions; index period of 1995-2009 for IHD events <sup>a</sup>	<u>Women</u> Overall: <b>0.66 (0.60-0.73)</b> Diagnosed with depression ≤180 days prior to IHD: same as women in general (data NR) Diagnosed with depression >180 days prior to IHD: <b>0.63 (0.56-0.71)</b>	NR
May 2009 (Intermountain Heart Collaborative Study) (N = 7719)	ICD codes	HR (95% CI) for association between heart failure and post-CAD depression; mean 5.6-year and 6.1-year follow-ups for all study patients and hospitalized/outpatient pharmacy cohort, respectively <sup>b</sup>	<u>Men</u> Overall: <b>0.67 (0.62-0.73)</b> Diagnosed with depression ≤180 days prior to IHD: <b>2.07 (1.35-3.18)</b> Diagnosed with depression >180 days prior to IHD: <b>0.62 (0.55-0.68)</b>	NR
Whooley 2008 (Heart and Soul Study) (N = 1017)	DIS was used to diagnose MDD; PHQ-9 ≥10 indicated symptoms of depression	HR (95% CI) for risk of cardiovascular events in patient with CHD; mean 4.8-year follow-up	<u>Risk of cardiovascular events according to DIS<sup>d</sup></u> Past-month MDD: 1.08 (0.82-1.44); p = 0.56 Past-year MDD: 1.12 (0.86-1.46); p = 0.39 Lifetime MDD: 0.98 (0.78-1.23); p = 0.86	Any cardiovascular events per each SD increase in depressive symptom score: 1.03 (0.92-1.16); p = 0.53 <sup>f</sup>

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
<u>With vs. without depressive symptoms according to PHQ-9 scores<sup>e</sup></u>				
Risk of any cardiovascular events: 1.05 (0.79-1.40); p = 0.75				
Risk of heart failure: 1.18 (0.78-1.80)				
Risk of MI: 0.98 (0.58-1.64)				
Risk of stroke or TIA: 1.47 (0.70-3.11)				

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences (p < 0.05) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, somatic comorbidity, and calendar year.

<sup>b</sup> Adjusted for age, diabetes, renal failure, follow-up MI, ACE-I, and diuretic therapy; among those with follow-up medication information, variables included age, diabetes, renal failure, ARB therapy, ACE-I, and diuretic therapy.

<sup>c</sup> Subgroups with available follow-up medication information.

<sup>d</sup> Adjusted for age.

<sup>e</sup> Adjusted for age (per 10-year increase), history of MI, stroke, diabetes, heart failure, LVEF per 10% increase, inflammation, log C-reactive protein per SD increase, smoking status, medication adherence, and physical activity.

<sup>f</sup> Adjusted for age, comorbid conditions, LVEF, log C-reactive protein, smoking, medication non-adherence, and physical activity.

ACE-I, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CAD, coronary artery disease; CI, confidence interval; DCRS, Danish Civil Registration System; DIS, Diagnostic Interview Schedule; HR, hazard ratio; ICD, International Classification of Diseases; IHD, ischemic heart disease; IRR, incident rate ratio; LVEF, left ventricular ejection fraction; MDD, Major depressive disorder; MI, myocardial infarction; NR, not reported; PHQ, Patient Health Questionnaire; SD, standard deviation; TIA, transient ischemic attack.

### Supplementary Table 19. Summary of studies assessing the association between depression and post-acute coronary syndrome events

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Davidson 2010 (N = 453)	DSM-IV MDD criteria assessed using diagnostic interview	HR (95% CI) for 12-month MACE and all-cause mortality; mean 10.4-month follow-up <sup>a</sup>	MDE: <b>1.48 (1.07-2.04)</b> ; p = 0.02 Antidepressant use: <b>1.34 (1.03-1.74)</b> ; p = 0.02 <sup>b</sup>	BDI score <5 vs. ≥10: 1.23 (0.94-1.62); p = 0.14



Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Frasure-Smith 2007; Frasure-Smith 2008 (ESCAPE) (N = 741)	DSM-IV MDD criteria assessed using SCID; BDI ≥14 indicates elevated depressive symptoms	HR and OR (95% CI) for time to first and subsequent MACE in patients assessed 2 months after ACS; followed-up every 6 months for 2 years	<u>Time to first MACE after ACS (HR)<sup>c</sup></u> SCID Overall: <b>2.38 (1.33-4.26); p = 0.004</b> Men: <b>3.17 (1.58-6.36); p = 0.001</b> Women: 1.24 (0.43-3.63); p = 0.69 <u>BDI-II ≥14</u> Overall: <b>1.74 (1.17-2.59); p = 0.007</b> Men: <b>1.72 (1.07-2.77); p = 0.024</b> Women: 1.08 (0.47-2.48); p = 0.85 <u>MACEs in subsequent 2 years after ACS (OR)<sup>d</sup></u> SCID-diagnosed: <b>2.34 (1.18-4.63); p = 0.02</b> BDI-II ≥14: <b>1.63 (1.05-2.54); p = 0.03</b>	<u>Time to first MACE after ACS (HR)<sup>e</sup></u> <u>Continuous BDI-II score</u> Overall: <b>1.20 (1.01-1.42); p = 0.041</b> Men: 1.18 (0.97-1.44); p = 0.11 Women: 0.87 (0.56-1.34); p = 0.52 <u>MACEs in subsequent 2 years after ACS (OR)<sup>d</sup></u> Continuous BDI-II score: 1.19 (0.95-1.49); p = 0.14
Goodman 2008 (COPEs) (N = 88)	DSM-IV MDD criteria assessed using DISH; BDI used to assess comorbid depressive symptom severity	β ± SE predicting CAD severity post-ACS in incident or recurrent MDD; lifetime history assessed <sup>f,g</sup>	Comorbid, in-hospital MDD: 0.17 ± 0.11; p = 0.12 History of MDD: 0.25 ± 0.26; p = 0.33 Comorbid MDD × history of MDD: <b>0.28 ± 0.13; p = 0.04</b>	NR
Ossola 2018 (N = 266)	DSM-IV MDD criteria assessed using PRIME-MD and psychiatric interview; HADS was also used	HR (95% CI) for the predictors of post-ACS MACE time to event; 24-month follow-up	HADS depression: 0.923 (0.817-1.042); p = 0.195 Incident depression: <b>2.590 (1.321-5.078); p = 0.006</b> Development of a depressive episode during the follow-up period predicting recurrent MACE: <b>2.449 (1.26-4.75); p = 0.008</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences (p < 0.05) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, Charlson comorbidity index score, GRACE risk score, LVEF, and antidepressant use at discharge.

<sup>b</sup> Adjusted for age only.

<sup>c</sup> Unadjusted.

<sup>d</sup> Adjusted for age, sex, years of education, current daily smoker, previous MI, CABG surgery or angioplasty, LVEF <45%, CABG surgery during index hospitalization, ≥1 coronary vessels with ≥50% blockage after index revascularization, BMI, fasting triglyceride level, DBP, calcium channel blockers, ACE-Is, and statins.

<sup>e</sup> Only the data for men were adjusted for years of education, marital status, current daily smoker, coronary bypass surgery, ≥1 coronary vessel with ≥50% blockage after index revascularization, BMI, fasting triglyceride level, fasting glucose level, fasting HDL level, diastolic blood pressure, beta-blockers, calcium channel blockers, ACE-Is, statins, and long-acting nitrates. The overall group and women-only data were unadjusted.

<sup>f</sup> Incident MDD is defined as in-hospital MDD and negative for history of MDD. Recurrent MDD is defined as in-hospital MDD and a positive history of MDD.

<sup>g</sup> Adjusted for age, sex, and ethnicity.

ACE-I; angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; BDI, Beck Depression Inventory; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; COPEs, Coronary Psychosocial Patient Evaluation Study; DPB, diastolic blood pressure; DISH, Depression Interview and Structured Hamilton; DSM, Diagnostic and Statistical Manual of Mental Disorders; ESCAPE, Epidemiological Study of Acute Coronary Syndromes and the Pathophysiology of Emotions; GRACE, Global Registry of Acute Coronary Events; HADS, Hospital Anxiety and Depression Scale; HDL, High density lipoprotein; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac event; MDD, Major depressive disorder; MDE, Major depressive episode; MI, myocardial infarction; NR, not reported; OR, odds ratio; PRIME-MD, Primary Care Evaluation of Mental Disorders; SCID, Structured Clinical Interview for DSM-IV disorders; SE, standard error.

## MI

**Supplementary Table 20. Summary of studies assessing the association between depression and MI incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Farmer 2008 (N = 2430)	Interviews using SCAN version 2.1; DSM-IV-TR or ICD codes used to assess recurrence	OR (95% CI) for MI in patients with recurrent depression; lifetime history assessed	NR	Recurrent: 2.70 (1.24-5.87); p = 0.17 <sup>a</sup>
Jakobsen 2008 (N = 328,349)	ICD codes	IRR (95% CI) for incidence of acute MI; up to 24-year follow-up <sup>b</sup>	<b>1.16 (1.10-1.22); p &lt; 0.0001</b>	NR
Janszky 2007 (SHEEP) (N = 4138)	ICD codes	OR (95% CI) for an acute MI case in patients who had a hospital discharge diagnosis of	All depression: <b>2.1 (1.1-4.2)<sup>c</sup></b> Psychotic depression only: <b>5.0 (1.7-15.2)<sup>d</sup></b>	<u>Based on recurrence of depression (number of hospitalizations)</u> 1: <b>2.5 (1.2-4.8)</b> 2-3: 2.6 (1.0-6.4) >3: <b>6.8 (1.5-31.3)</b>

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Janszky 2010 (N = 49,321)	ICD codes	depression; 26-year exposure window HR (95% CI) for risk of acute MI; mean 37-year follow-up <sup>e</sup>	1.20 (0.75-1.90)	NR
Mathur 2016 (N = 524,952)	Diagnostic Read codes	HR (95% CI) for association between depression or antidepressant use and non-fatal MI; 10-year follow-up <sup>f</sup>	Depression at baseline: <b>1.21 (1.05-1.39); p &lt; 0.01</b> Antidepressant use at baseline: <b>1.20 (1.08-1.34); p &lt; 0.0001</b>	NR
Niranjan 2012 (NESARC) (N = 9174)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for association between MDD and MI; lifetime history assessed	MDD vs. no MDD: <b>1.57 (1.12-2.21); p &lt; 0.01<sup>g</sup></b> MDD with atypical features vs. without: 1.13 (0.48-2.62) <sup>h</sup>	NR
<b>Meta-analyses</b>				
Nicholson 2006 (N = 146,538)	Self-completed questionnaire, diagnostic interview, physician diagnosis, anti-depressant medication, or self-reported diagnosis	Pooled RR (95% CI) for incidence of fatal and non-fatal MI	<b>1.95 (1.51-2.51)<sup>i</sup></b>	NR
Van der Kooy 2007 (N ≈ 80,000)	Depressive symptoms or disorders	Pooled RR (95% CI) for MI in patients with depressive symptoms or disorders	<b>1.60 (1.34-1.92)</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Wu 2016 (N = 323,709)	Clinical diagnosis or standardized psychometric tool	Pooled HR (95% CI) of fatal and non-fatal MI associated with depression	<b>1.31 (1.09-1.57)</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> p-value corrected for multiple testing; prior to correction it was significant at 0.012.

<sup>b</sup> Adjusted for age and sex.

<sup>c</sup> Adjusted for age, sex, hospital catchment area, education, smoking, obesity, alcohol consumption, physical activity, triglycerides, HDL and total cholesterol, PAI-1, fibrinogen, hypertension, and diabetes.

<sup>d</sup> Adjusted for age, sex, and hospital catchment area.

<sup>e</sup> Adjusted for smoking, body length, diabetes, SBP, alcohol consumption, physical activity, father's occupation, family history of CHD, geographic area, body length, father's occupation, and geographic area.

<sup>f</sup> Adjusted for age, sex, ethnicity, cardiovascular risk, medication use, deprivation, and presence of anxiety at baseline.

<sup>g</sup> Adjusted for age, sex, ethnicity, education, family income, and health insurance.

<sup>h</sup> Adjusted for age, sex, ethnicity, education, household income, profession, marital status, access to health insurance, BMI, smoking status, alcohol use pattern, stimulant use, and cocaine use.

<sup>i</sup> Data are unadjusted.

AUDADIS, Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; HDL, high-density lipoprotein; HR, hazard ratio; ICD, International Classification of Diseases; IRR, incident rate ratio; MDD, Major depressive disorder; MI, myocardial infarction; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NR, not reported; OR, odds ratio; PAI-1, plasminogen activator inhibitor; RR, risk ratio; SBP, systolic blood pressure; SCAN, Schedules for the Clinical Assessment of Neuropsychiatry; SHEEP, Stockholm Heart Epidemiology Program.

### Supplementary Table 21. Summary of studies assessing the association between depression and post-MI events

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
De Jonge 2006 (DepreMI) (N = 468)	CIDI	HR (95% CI) for cardiovascular events post-MI; mean 2.5-year follow-up <sup>a</sup>	Incident post-MI depression: <b>1.76 (1.06-2.93)</b> Non-incident post-MI depression: 1.39 (0.74-2.61)	NR
Huffman 2008 (N = 129)	DSM-IV MDD criteria assessed using SCID; BDI-II	OR (95% CI) for the development of in-hospital post-MI cardiac	<u>SCID/BDI-defined MDD</u> Recurrent chest pain with ischemia: NS/NS	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
	≥14 indicates threshold for clinically significant symptoms	complications; current MDD (within last 2 weeks) <sup>b</sup>	Ventricular arrhythmia: <b>3.07 (1.06-8.88); p = 0.039/NS</b> Ventricular arrhythmia requiring intervention: <b>26.53 (1.11-632.9); p = 0.043/1.11 (1.08-1.16); p = 0.024</b> CHF: <b>15.45 (1.81-161.7); p = 0.022/NS</b> Reinfarction: <b>8.44 (1.34-53.20); p = 0.023/NS</b>	
Mohamed 2019 (N = 6,738,757)	ICD codes	OR (95% CI) of in-hospital post-MI complications and outcomes; 10-year study period <sup>c</sup>	<u>MACCE</u> Total: <b>0.86 (0.85-0.88); p &lt; 0.001</b> Women: <b>1.08 (1.05-1.11); p &lt; 0.001</b> <u>Acute stroke/TIA</u> Total: <b>0.84 (0.81-0.86); p &lt; 0.001</b> Women: <b>1.35 (1.27-1.43); p &lt; 0.001</b> <u>All-cause bleeding</u> Total: <b>0.97 (0.95-0.98); p &lt; 0.001</b> Women: <b>1.13 (1.09-1.16); p &lt; 0.001</b>	NR
Reese 2011 (ENRICHD ancillary study) (N = 766)	DSM-IV MDD criteria assessed using DISH; BDI was used to assess severity of depression	HR (95% CI) for the effect of depression on time to first cardiac hospitalization; follow-up every 6 months for up to 42 months <sup>d</sup>	Major vs. no depression: <b>2.54 (1.84-3.53); p &lt; 0.001</b> Minor vs. no depression: <b>2.22 (1.59-3.08); p &lt; 0.001</b> Major vs. minor depression: 1.15 (0.81-1.62); p = 0.43	BDI score was significantly associated with time to rehospitalization: <b>1.02 (1.0-1.04); p = 0.02<sup>e</sup></b>
<b>Meta-analysis</b>				
Meijer 2011 (N = 16,889)	Validated depression rating scale or structured diagnostic interview	Pooled OR (95% CI) post-MI cardiac events	Overall: <b>1.59 (1.37-1.85); p &lt; 0.001</b> Interview-based instruments to assess depression: 1.96 (0.99-3.89); p < 0.05 Self-report instruments to assess depression: <b>1.53 (1.35-1.73); p &lt; 0.001</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences (p < 0.05) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, education level, LVEF <40%, and revascularization.

<sup>b</sup> Adjusted for peak troponin T and LVEF, plus other demographic, medical, and psychological variables that were significant in a univariate analysis (differed for each outcome).

<sup>c</sup> Adjusted for age, sex, weekend admission, primary expected payer, median household income, dyslipidemia, smoking status, previous acute MI, previous CABG, history of IHD, previous PCI, previous CVA, family history of CAD, shock during hospitalization, receipt of PCI during admission, bed size of hospital, region of hospital, location/teaching status of hospital, thrombocytopenia, Charlson comorbidity index and 27 AHRQ comorbidities.

<sup>d</sup> Adjusted for the imputed ENRICHHD all-cause mortality risk score and a random frailty term for study site.

<sup>e</sup> Unadjusted. Every 1-point increase on the BDI was associated with a 2% increase in the risk of rehospitalization in the depressed subgroup.

AHRQ, Agency for Healthcare Research and Quality; BDI, Beck Depression Inventory; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CIDI, Composite International Diagnostic Interview; CVA, cerebrovascular accident; DepreMI, Depression after Myocardial Infarction; DISH, Depression Interview and Structured Hamilton; DSM, Diagnostic and Statistical Manual of Mental Disorders; ENRICHHD, Enhancing Recovery and Coronary Heart Disease; HR, hazard ratio; ICD, International Classification of Diseases; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MACCE, Major acute cardiovascular and cerebrovascular events; MDD, Major depressive disorder; MI, myocardial infarction; NR, not reported; NS, not significant; OR, odds ratio; PCI, percutaneous coronary intervention; SCID, Structured Clinical Interview for DSM-IV disorders; TIA, Transient ischemic attack.

## Stroke

**Supplementary Table 22. Summary of studies assessing the association between depression and stroke incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Almas 2015 (PART) (N = 10,341)	DSM-IV criteria using MDI	OR (95% CI) stroke; 10- to 13-year follow-up <sup>a,b</sup>	Overall: <b>1.7 (1.1-2.6)</b>	Mild: 1.5 (0.7-3.0) Moderate: <b>2.2 (1.1-4.3)</b> Severe: 1.5 (0.8-2.9)
Brunner 2014 (Whitehall II) (N = 10,297)	Caseness $\geq 5$ on GHQ-30 or $\geq 16$ on CES-D	HR (95% CI) incidence of stroke events; 24-year follow-up <sup>c</sup>	5 years (no lag): <b>1.60 (1.13-2.26); P = .009</b> 10 years (5-year lag): 0.94 (0.64-1.37); P = .74 ~18-year analysis: 1.21 (0.61-2.42); P = .89	<u>Multiple episodes</u> 5 years (no lag): 1.33 (0.88-2.02) 10 years (5-year lag): 0.81 (0.49-1.34) <u>Cumulative GHQ caseness</u> 1-2 times: <b>0.48 (0.26-0.89)</b> 3-4 times: 0.76 (0.30-1.94) P trend = .07
Davydow 2015 (Health and Retirement Study) (N = 7031)	CES-D $\geq 4$ or Medicare claims based on ICD codes	OR (95% CI) ischemic stroke; mean 6.8-year follow-up <sup>d</sup>	Depression alone: 1.09 (0.85-1.38) With cognitive impairment without dementia: <b>1.65 (1.24-2.18); P &lt; .001</b> With dementia: 1.16 (0.82-1.65)	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Farmer 2008 (N = 2430)	Interviews using SCAN version 2.1; DSM-IV-TR or ICD codes used to assess recurrence	OR (95% CI) stroke in people with recurrent depression; lifetime history assessed	NR	Overall: 3.33 (0.97-11.50)
Graham 2019 (N = 134,860)	Participant interview	HR (95% CI) risk of adverse stroke events; median 63-month follow-up <sup>e</sup>	<u>MDD only</u> Overall: 1.20 (0.89-1.63); <i>P</i> = .24 Men: 1.49 (0.97-2.29); <i>P</i> = .07 Women: 0.99 (0.64-1.53); <i>P</i> = .98 <u>Hypertension + MDD</u> Overall: <b>1.37 (1.04-1.79)</b> ; <i>P</i> = .02 Men: 1.20 (0.83-1.74); <i>P</i> = .33 Women: <b>1.62 (1.08-2.42)</b> ; <i>P</i> = .02	NR
Hamano 2015 (N = 326,229)	ICD codes	OR (95% CI) incident stroke; 3-year follow-up <sup>f</sup>	Overall: <b>1.22 (1.08-1.38)</b> Men: <b>1.45 (1.19-1.77)</b> Women: 1.11 (0.95-1.30)	NR
Karakus 2011 (Health and Retirement Study) (N = 3645)	CES-D ≥3	OR heart problems/stroke; 12-year follow-up <sup>g</sup>	<b>1.696</b> ; <i>P</i> = .004	NR
Kohler 2013 (AgeCoDe) (N = 2854)	GDS ≥6	HR (95% CI) incident stroke; follow-up every 1.5 years for 6 years <sup>h</sup>	Overall: 0.90 (0.55-1.48); <i>P</i> = .901 Women: 1.02 (0.57-1.80); <i>P</i> = .958 Men: 0.61 (0.21-1.78); <i>P</i> = .363 75-79 years: 0.69 (0.33-1.45); <i>P</i> = .324 80-84 years: 1.50 (0.72-3.16); <i>P</i> = .281 ≥85 years: 1.02 (0.19-5.44); <i>P</i> = .977	Depression severity groups defined by GDS score categories or continuous GDS did not show significant associations with stroke

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Liebetrau 2008 (N = 401)	DSM-III MDD criteria using psychiatrist interview	RR (95% CI) incidence of stroke; 3-year follow-up <sup>i</sup>	<u>All participants</u> Overall: <b>2.6 (1.5-4.6)</b> ; <i>P</i> = .0009 Women: <b>2.9 (1.6-5.3)</b> Men: 1.4 (0.3-6.8) Use of antidepressants: 2.0 (0.6-5.3) <sup>j</sup> <u>No dementia</u> Overall: <b>2.4 (1.2-4.6)</b> Women: <b>2.8 (1.4-5.7)</b> Men: 0.8 (0.1-6.5) <u>Dementia</u> Overall: <b>3.8 (1.2-9.8)</b> Women: <b>3.2 (1.0-11.6)</b> Men: NR	NR
Marijnissen 2014 (Longitudinal Aging Study Amsterdam) (N = 2050)	CES-D ≥16	HR (95% CI) risk of stroke; follow-up interviews every 3 years for 9 years	No cardiac disease: <b>42.6 (5.23-347)</b> ; <i>P</i> < .001 With cardiac disease: 0.37 (0.01-26.3); <i>P</i> = .649	<u>CES-D as a continuous measure</u> <b>No cardiac disease: 1.12 (1.03-1.22)</b> ; <i>P</i> = .008 With cardiac disease: 0.97 (0.79-1.20); <i>P</i> = .776
Mathur 2016 (N = 524,952)	Diagnostic Read codes	HR (95% CI) stroke; 10-year study period <sup>k</sup>	Depression: 1.29 (1.00-1.66) Antidepressant use: 1.01 (0.82-1.24)	NR
Nabi 2010 (HeSSup) (N = 23,282)	BDI ≥10	HR (95% CI) incident cerebrovascular events; 7-year follow-up <sup>l</sup>	Overall: 0.87 (0.57-1.32)	Continuous BDI per 1-unit increase: 0.98 (0.96-1.01) Mild symptoms: 0.82; <i>P</i> = .435 Moderate symptoms: 0.79; <i>P</i> = .577 Severe symptoms: 1.97; <i>P</i> = .255
Pan 2011a (Nurses' Health Study) (N = 80,574)	MHI-5 ≤52; clinical depression diagnosed by physician; antidepressant use	HR (95% CI) incident stroke and subtypes of stroke; follow-up every 2 years for 6 years <sup>m</sup>	Total stroke: <b>1.29 (1.13-1.48)</b> Hemorrhagic stroke: 1.20 (0.80-1.79) Ischemic stroke: 1.11 (0.91-1.35) Stroke of unknown type: <b>1.63 (1.31-2.03)</b>	NR



Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Surtees 2008a (EPIC-Norfolk) (N = 20,627)	DSM-IV MDD criteria using HLEQ	HR (95% CI) fatal and nonfatal incident stroke; median 8.5-year follow- up <sup>n</sup>	<u>Fatal and nonfatal</u> Overall: 1.08 (0.67-1.75) Men: 1.12 (0.52-2.42) Women: 1.03 (0.55-1.93) <u>Nonfatal</u> Overall: 1.18 (0.70-1.97) Men: 1.32 (0.61-2.88) Women: 1.06 (0.53-2.12)	<u>MHI-5 per SD decrease in scores</u> <i>Fatal and nonfatal</i> Overall: 1.11 (1.00-1.22) Men: 1.15 (1.00-1.32) Women: 1.08 (0.94-1.23) <i>Nonfatal</i> Overall: 1.10 (0.99-1.22) Men: 1.14 (0.98-1.33) Women: 1.07 (0.92-1.25)
Wium- Andersen 2019 (N = 99,368)	ICD codes; MDI ≥25	HR (95% CI) subsequent stroke; median 20.6-year follow- up	<u>Pooled cohort<sup>o</sup></u> <b>1.94 (1.63-2.30); P &lt; .001</b> <u>Metropolit cohort<sup>p</sup></u> Overall: <b>3.45 (2.30-5.16)</b> Hospital diagnosis: 1.62 (0.76-3.42) Self-reported: <b>1.47 (1.09-1.98)</b> MDI ≥25: <b>1.71 (1.04-2.82)</b>	NR
<b>Meta-analyses</b>				
Barlinn 2014 28 studies (N = 681,139)	Neuropsychological mood scale or neuropsychiatric evaluation complying with DSM-III/IV or ICD codes	Pooled RR (95% CI) risk of incident stroke	Overall: <b>1.40 (1.27-1.53); P &lt; .0001</b> Restricted to studies that assessed all stroke subtypes: <b>1.50 (1.21-1.86);</b> <b>P &lt; .0001</b>	NR
Correll 2017 30 studies N = 3,211,768	ICD codes or diagnoses according to DSM- III/IV/5 criteria	Pooled RR (95% CI) risk of cerebrovascular disease in people with MDD	Longitudinal studies: <b>2.04 (1.05-3.96);</b> <b>P = .04</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Van der Kooy 2007 28 studies (N ≈ 80,000)	Depressive symptoms or disorders	Pooled RR (95% CI) stroke in people with depressive symptoms or disorders	Overall: <b>1.43 (1.17-1.75)</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $P < .05$ ) are shown in bold font;  $P$  values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, socioeconomic status, BMI, history of IHD, stroke, hypertension, diabetes, smoking, physical activity, and hazardous alcohol consumption.

<sup>b</sup> All participants from wave 1 (1998-2000) were followed-up in wave 3 (2010) for the occurrence of CVD. Data from the National Patient Register had their follow-up from 2008 to 2011.

<sup>c</sup> Adjusted for age, sex, and ethnicity.

<sup>d</sup> Adjusted for age categorized by deciles, sex, ethnicity, education, marital/partnered status, dual Medicare-Medicaid eligibility, MI, cerebrovascular disease, CHF, valvular disease, pulmonary circulation disease, peripheral vascular disease, other neurological disorders, diabetes mellitus, hypertension, alcohol use, and smoking status.

<sup>e</sup> Adjusted for age, sex, Townsend score, age of leaving full-time education, ethnicity, history of diabetes, history of hypercholesterolemia, BMI, smoking history, alcohol use, SBP, sedentary hours per day, physical activity, and psychotropic medication use.

<sup>f</sup> Adjusted for age, country of origin, education, family income, and family history of comorbidities.

<sup>g</sup> Adjusted for age at baseline, sex, ethnicity, marital status, education level, BMI, cigarette smoking, functional limitations index, self-report of limited ability to work, household income, and excessive alcohol drinking.

<sup>h</sup> Adjusted for age group, sex, marital status, level of education, smoking, hypertension, MI, diabetes, peripheral artery disease, TIA, hypercholesterolemia, hyperlipidemia, ApoE status, mobility, activities of daily living impairment, level of alcohol consumption, and mild cognitive impairment status.

<sup>i</sup> Sex-adjusted where men and women are analyzed together.

<sup>j</sup> Results did not change after controlling for depression at age 85 and excluding individuals with dementia.

<sup>k</sup> Adjusted for age, sex, ethnic group, cardiovascular risk, medication use, deprivation, and presence of anxiety at baseline.

<sup>l</sup> Adjusted for age, sex, education, alcohol consumption, sedentary lifestyle, smoking, obesity, hypertension or diabetes, and incident CHD or incident cerebrovascular disease.

<sup>m</sup> Adjusted for age, marital status, parental history of MI, ethnicity, physical activity level, BMI, alcohol consumption, smoking status, menopausal status, postmenopausal hormone therapy, current aspirin use, current multivitamin use, Dietary Approaches to Stop Hypertension dietary score, history of hypertension, hypercholesterolemia, diabetes, cancer, and heart disease. Note: any diagnosis of depression was defined as MHI-5  $\leq 52$ , physician diagnosis, or antidepressant use; current clinical depression was defined as physician diagnosis or antidepressant use.

<sup>n</sup> Adjusted for age, sex, cigarette smoking, SBP, total cholesterol, obesity, preexisting MI, diabetes, social class, education, hypertension treatment, family history of stroke, and antidepressant medication use.

<sup>o</sup> Adjusted for age, sex, education, marital status, cohort, calendar year, alcohol use, smoking status, physical activity, BMI, SBP, total cholesterol, statin use, and stroke or IHD.

<sup>p</sup> Adjusted for education, daily alcohol use, smoke status, physical activity, and BMI.

Abbreviations: AgeCoDe, German Study on Ageing, Cognition, and Dementia in Primary Care Patients; ApoE, apolipoprotein E; BDI, Beck Depression Inventory; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CVD, cardiovascular disease; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; EPIC, European Prospective Investigation into Cancer; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; HeSSup, Health and Social Support; HLEQ, Health and Life Experiences Questionnaire; HR, hazard ratio; ICD, International Classification of Diseases; IHD, ischemic heart disease; MDD, major depressive disorder; MDI, Major Depression Inventory; MHI-5, Mental Health Inventory-5; MI, myocardial infarction; NR, not reported; OR, odds ratio; PART, Psykisk hälsa, Arbeta och Relationer; RR, risk ratio; SBP, systolic blood pressure; SCAN, Schedules for the Clinical Assessment of Neuropsychiatry; SD, standard deviation; TIA, transient ischemic attack.

**Supplementary Table 23. Summary of studies assessing the association between depression and stroke severity/recovery**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Schmid 2011 (Activate-Initiate-Monitor study) (N = 174)	Decrease in PHQ-9 from baseline to 12 weeks of at least 50% or a 12-week PHQ-9 <10 indicates depression improvement	Association between depression and post-stroke functional independence; 12-week follow-up	Overall cohort: baseline depression was not associated with 12-week functional outcome (data NR)	NR
Willey 2010 (NOMASS) (N = 340)	HAM-D	OR (95% CI) of the association between post-stroke depressed mood and disability after stroke; follow-up every 6 months for 2 years then annually for 5 years <sup>a</sup>	<u>1 year</u> Severe vs. no disability: <b>2.91 (1.07-7.91)</b> Moderate vs. no disability: 1.13 (0.52-2.48) <u>2 years</u> Severe vs. no disability: <b>3.72 (1.29-10.71)</b> Moderate vs. no disability: 0.98 (0.43-2.26)	NR
Wulsin 2012 (GCNKSS) (N = 460)	CIDI for lifetime depression; CES-D ≥10 indicates current depression	OR (95% CI) of decreased 3- and 12-month modified Rankin Scale >2 (post-ischemic stroke functional status); 3- and 12-month follow-up <sup>b</sup>	<u>Any depression</u> 3 months: <b>2.42 (1.36-4.29)</b> 12 months: <b>3.31 (1.82-6.02)</b> <u>History of depression</u> 3 months: <b>2.35 (1.03-5.35)</b> 12 months: <b>3.33 (1.41-7.86)</b> <u>CES-D depression</u> 3 months: 2.04 (0.98-4.26) 12 months: <b>2.95 (1.36-6.41)</b> <u>History and CES-D</u> 3 months: <b>3.09 (1.38-6.94)</b> 12 months: <b>3.80 (1.64-8.80)</b>	NR
<b>Meta-analysis</b>				
Bloch 2019 (N = 3273)	Any assessment of	OR (95% CI) of severe long-term	Overall: <b>2.16 (1.70-2.77)</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
	depression, depression severity, or depressive symptoms at baseline or before follow-up	disability for patients with stroke (post-stroke recovery/functional outcomes) <sup>c</sup>		

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

EPIC-Norfolk, which assessed incidence of fatal stroke in a population-based cohort, is shown in Supplementary Table 13.

<sup>a</sup> Adjusted for age, ethnicity, completing a high school education, having <3 friends, being unmarried, having Medicaid or no insurance, stroke severity, physical activity, CAD, and diabetes.

<sup>b</sup> Adjusted for age, race, sex, baseline disability, and stroke severity.

<sup>c</sup> The ORs included in the meta-analytic model were converted into logarithmic ORs (log ORs) as a common, standardized effect size. The log transformation makes the OR symmetric around zero and yields corresponding sampling distributions that are closer to normality.

BMI, body mass index; CAD, coronary artery disease; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; CIDI, Composite International Diagnostic Interview; GCNKSS, Greater Cincinnati/Northern Kentucky Stroke Study; HAM-D, Hamilton Depression Rating Scale; NOMASS, Northern Manhattan Stroke Study; NR, not reported; OR, odds ratio; PHQ, Patient Health Questionnaire; SBP, systolic blood pressure.

## Metabolic/Endocrine

### Metabolic syndrome

**Supplementary Table 24. Summary of studies assessing the association between depression and metabolic syndrome incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
Block 2016 (SHIP-0; SHIP-TREND-0) (N = 8040)	DSM-IV MDD criteria assessed using CID-S or M-CIDI	OR (95% CI) for association between depression and metabolic syndrome according to NCEP/ATP III criteria; lifetime history assessed <sup>a</sup>	<u>Females</u> SHIP-0, depression at syndromal level: 1.14 (0.83-1.56) SHIP-TREND-0 depression at syndromal level: 1.14 (0.90-1.44) MDD lifetime: 1.14 (0.87-1.49) <u>Males</u> SHIP-0, depression at syndromal level: <b>1.53 (1.06-2.21); p ≤ 0.05</b> SHIP-TREND-0 depression at syndromal level: 1.15 (0.88-1.50) MDD lifetime: 1.30 (0.97-1.73)	<u>Recurrent MDD</u> Females: 1.20 (0.88-1.62) Males: 1.30 (0.91-1.87)
Goldbacher 2009 (SWAN) (N = 429)	DSM-IV MDD criteria assessed using SCID-IV	OR/HR (95% CI) for history or current MDE as a predictor of metabolic syndrome according to NCEP/ATP III criteria; 7-year follow-up <sup>b</sup>	GEE model: OR 1.61 (0.92-2.81) Survival analysis: HR 1.54 (0.93-3.40)	Recurrent depression: HR 1.83 (0.99-4.76)
Lasserre 2017 (CoLaus/PsyCoLaus) (N = 3056)	DSM-IV MDD criteria assessed using DIGS	OR (95% CI) for incident metabolic syndrome; mean 5.5-year follow-up <sup>c</sup>	<u>By MDD subtype</u> Atypical: <b>2.49 (1.30-4.77); p &lt; 0.01</b> Melancholic: 1.45 (0.78-2.69) Unspecified: 1.44 (0.83-2.49)	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age categories, marital status, education, employee status, smoking, physical inactivity, and risky alcohol consumption.

<sup>b</sup> Adjusted for baseline age and race.

<sup>c</sup> Adjusted for socio-demographic characteristics, length of follow-up, behavioral factors, comorbid disorders, early trauma, depression status at baseline and follow-up, medication at baseline, cardio-metabolic risk factors at baseline, inflammatory markers, and adipokine concentrations at baseline. ATP, Adult Treatment Panel; CI, confidence interval; CID-S, Composite International Diagnostic-Screener; DIGS, Diagnostic Interview for Genetic Studies; DSM, Diagnostic and Statistical Manual of Mental Disorders; GEE, generalized estimating equation; HR, hazard ratio; M-CIDI, Munich-Composite International Diagnostic Interview; MDD, major depressive disorder; MDE, major depressive episode; NCEP, National Cholesterol Education Program; NR, not reported; OR, odds ratio; SCID, Structured Clinical Interview for DSM-IV disorders; SHIP, Study of Health In Pomerania; SWAN, Study of Women's Health Across the Nation.

### *Association Between Depression and Metabolic Syndrome Severity*

Only the Hiles 2016 study (N = 2776) assessed the impact of depression on metabolic syndrome severity according to the number of metabolic syndrome abnormalities present. Both use of antidepressants and depression severity by IDS score at year 0 were significantly associated with worsening of metabolic syndrome at year 2 ( $\beta \pm SE$ :  $0.0731 \pm 0.0308$ ;  $p = 0.017$  and  $0.0027 \pm 0.0010$ ;  $p = 0.006$ , respectively), but antidepressant use/IDS score at year 2 were not significantly associated with disease worsening at year 6.

### Hyperlipidemia

#### *Association Between Depression and Risk of Incident Hyperlipidemia*

Both the Block 2016 (N = 8040) and Goldbacher 2009 (N = 429) studies reporting metabolic syndrome outcomes in Supplementary Table 24 also reported individual symptom component data for hyperlipidemia. Both MDD (OR 1.33; 95% CI: 1.01-1.74;  $p \leq 0.05$  for lifetime MDD; OR 1.42; 95% CI: 1.01-2.00;  $p \leq 0.05$  for recurrent MDD) and depression at the syndromal level (OR 1.67; 95% CI: 1.18-2.37;  $p \leq 0.05$  for SHIP-0 and OR 1.29; 95% CI: 1.01-1.64;  $p \leq 0.05$  for SHIP-TREND-0) were significantly associated with hyperlipidemia (high triglycerides) in a subgroup of men only, whereas no significant relationship was observed in women (OR 1.11; 95% CI: 0.85-1.44 for lifetime MDD; OR 1.17; 95% CI: 0.87-1.58 for recurrent MDD; OR 1.02; 95% CI: 0.73-1.41 and OR 1.16; 95% CI: 0.92-1.47 for depression at the syndromal level in SHIP-0 and SHIP-TREND-0, respectively) [Block 2016]. When stratified by age, this association in men somewhat paradoxically remained significant only for those in the older age category (50-82 years) with depression at the syndromal level, and only in men age 20-49 with recurrent MDD (OR 1.67; 95% CI: 1.03-2.72;  $p \leq 0.05$  for the age 20-49 subgroup compared with OR 1.40; 95% CI: 0.88-2.22 in the age 50-82 subgroup) [Block 2016]. By contrast, in the Goldbacher 2009 study (which did not stratify results by sex or age), results were similar to those of metabolic syndrome as there was no statistically significant association observed between depression and high triglycerides (HR 1.11; 95% CI: 0.78-1.83).

One additional study was identified by the SLR that assessed dyslipidemia in a retrospective analysis of a US medical claims database [Davis 2008; N  $\approx$  600,000]. This analysis, which assessed transitions between health states, showed that depression in the past year and in the past 1-2 years was associated with the transition from health to dyslipidemia (RR 2.3; 95% CI: 2.2-2.3 and RR

2.6; 95% CI: 2.5-2.7, respectively). Among patients with existing hypertension, the transition from hypertension alone to hypertension with dyslipidemia was similarly associated with depression (RR 1.5; 95% CI: 1.5-1.6 and RR 1.6; 95% CI: 1.5-1.8, respectively).

### Association Between Depression and Hyperlipidemia Severity

The Hiles 2016 study (N = 2776) also assessed individual components of metabolic syndrome, including high triglycerides. In this analysis, antidepressant use at year 0 was significantly associated with worsening of hypertriglyceridemia at year 2 ( $\beta \pm SE$ : 0.0272  $\pm$  0.0086;  $p = 0.002$ ), but antidepressant use at year 2 was not significantly associated with disease worsening at year 6 ( $\beta \pm SE$ : 0.0169  $\pm$  0.0108;  $p = 0.119$ ). No significant associations were noted between IDS and disease severity over either time period.

### Diabetes

**Supplementary Table 25. Summary of studies assessing the association between depression and diabetes severity**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
<b>Diabetes only</b>				
Brieler 2016 (PCPD Registry) (N = 1399)	ICD codes	OR (95% CI) for association with Type 2 diabetes HbA1c control vs. untreated depression; 5-year follow-up <sup>a</sup>	<u>GEE model</u> Treated depression: <b>1.95 (1.02-3.71); p &lt; 0.05</b> <u>Marginal multilevel linear regression model</u> Treated depression: -0.54 (-1.07-0.001)	NR
Dirmaier 2010 (DETECT) (N = 866)	DSQ and ICD	OR (95% CI) for problems with Type 2 diabetes glycemic control in patients with depression vs. no depression; 12-month follow-up <sup>b</sup>	Glycemic control at baseline: <b>1.71 (1.01-2.90); p &lt; 0.05</b> Glycemic control at follow-up, unadjusted: <b>2.1 (1.4-3.2); p &lt; 0.001</b> Glycemic control at follow-up, adjusted: <b>2.0 (1.1-3.7); p = 0.02</b>	NR
Katon 2013 (Pathways Epidemiologic Study) (N = 4119)	DSM-IV MDD criteria assessed using PHQ-9	HR (95% CI) for MDD for time to a hypoglycemic event; RR (95% CI) for number of hypoglycemic events; 5-year follow-up <sup>c</sup>	Time to a hypoglycemic event: <b>1.42 (1.03-1.96)</b> Number of hypoglycemic events: <b>1.34 (1.03-1.74)</b>	NR
Lin 2010 (Pathways)	DSM-IV MDD criteria	HR (95% CI) for microvascular or	<u>MDD</u> Microvascular: <b>1.36 (1.05-1.76)</b>	<u>Minor depression</u> Microvascular: 1.31 (0.98-1.74)



Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression severity
Epidemiologic Study) (N = 3723)	assessed using PHQ-9	macrovascular outcomes in patients with Type 2 diabetes; 5-year follow-up <sup>d</sup>	Macrovascular: 1.25 (1.00-1.54)	Macrovascular: 1.00 (0.79-1.27)
Sieu 2011 (Pathways Epidemiologic Study) (N = 2359)	DSM-IV MDD criteria assessed using PHQ-9	OR (95% CI)/HR (95% CI) for the association of baseline depression severity and incident diabetic retinopathy <sup>e</sup>	NR	<u>Per 1-point increase in PHQ-9</u> OR: <b>1.026 (1.002-1.051)</b> ; p = 0.033 HR: <b>1.025 (1.009-1.041)</b> ; p = 0.002
<b><i>Diabetes as a component of metabolic syndrome</i></b>				
Hiles 2016 (N = 2776)	MDD criteria assessed using CIDI	$\beta \pm SE$ for prospective association of antidepressant use with subsequent changes in fasting glucose at the next assessment; 6-year follow-up <sup>f</sup>	<u>Antidepressant use</u> 0-2 years: <b>0.0095 ± 0.0026</b> ; p < 0.001 2-6 years: -0.0007 ± 0.0028; p = 0.800	<u>IDS</u> 0-2 years: 0.0000 ± 0.0001; p = 0.598 2-6 years: 0.0002 ± 0.0001; p = 0.153

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences (p < 0.05) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for comorbidities (anxiety, obesity, hyperlipidemia, hypertension, vascular disease), health behaviors (referral to dietary education, smoking history, insulin prescription, other diabetic drug prescription), diabetes treatment, and demographics (age, race, sex, utilization).

<sup>b</sup> Adjusted for age, sex, marital and employment status, education, physical activity, BMI, smoking, drinking, duration of diabetes, and type of diabetes treatment.

<sup>c</sup> Adjusted for age, sex, race, education, marital status, prior hypoglycemic event, diabetes duration, insulin use, RxRisk score, hypertension diagnosis, diabetes type 1 or 2, diabetes complication score, BMI, current smoking, and physical activity.

<sup>d</sup> Adjusted for age, sex, race, education, marital status, any prior microvascular/macrovascular event, diabetes duration, treatment intensity, expected costs, hypertension, BMI, smoking, limited physical activity, and HbA1c.

<sup>e</sup> Adjusted for age, sex, race, education, and marital status, length of follow-up, duration of diabetes, diabetes treatment, hypertension, diabetes complications, enrollment status, exercise, smoking, BMI, and HbA1c.

<sup>f</sup> Adjusted for age, sex, education, baseline values of the outcome, smoking, alcohol use, and physical activity.

BMI, body mass index; CI, confidence interval; CIDI, Composite International Diagnostic Interview; DETECT, Diabetes Cardiovascular Risk Evaluation: Targets and Essential Data for Commitment of Treatment; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSQ, Depression Screening Questionnaire; GEE, generalized estimating equations; HR, hazard ratio; ICD, International Classification of Diseases; IDS, Inventory of Depressive Symptomatology; MDD, major depressive disorder; NR, not reported; OR, odds ratio; PCPD, Primary Care Patient Data; PHQ, Patient Health Questionnaire; RR, risk ratio; SE, standard error.

## Obesity

**Supplementary Table 26. Summary of studies assessing the association between depression and obesity incidence**

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
<b>Obesity only</b>				
Dave 2011 (N = 3229)	DSM-IV MDD criteria (National Comorbidity Survey); CES-D $\geq 10$ (National Longitudinal Survey of Youth)	Marginal effects $\pm$ SE for effects of MDD on overweight or obese status; lifetime history (National Comorbidity Survey) and 6-14-year follow-up (National Longitudinal Survey of Youth) <sup>a</sup>	<u>National Comorbidity Survey – Replication</u> <i>Males</i> Current MDD: 0.0053 $\pm$ 0.03 Past MDD: 0.0254 $\pm$ 0.03 Lifetime MDD: 0.0212 $\pm$ 0.03 <i>Females</i> Current MDD: 0.0201 $\pm$ 0.03 Past MDD: <b>0.0656 <math>\pm</math> 0.03; p &lt; 0.01</b> Lifetime MDD: <b>0.0624 <math>\pm</math> 0.02; p &lt; 0.01</b> <u>National Longitudinal Survey of Youth</u> <i>Between-effects model</i> All: 0.018 $\pm$ 0.053 Females: <b>0.076 <math>\pm</math> 0.040; p &lt; 0.05</b>	NR
Lasserre 2014 (CoLaus/ PsyCoLaus) (N = 3054)	DSM-IV MDD criteria assessed using DIGS	OR (95% CI) for incidence of obesity during follow-up by MDD status at baseline; mean 5.5-year follow-up <sup>b</sup>	<u>Current MDD</u> Atypical: <b>3.75 (1.24-11.35); p &lt; 0.05</b> Melancholic: 3.20 (0.75-13.64) Combined: 0.78 (0.09-7.05) Unspecified: 0.18 (0.02-1.50) <u>Remitted MDD</u> Atypical: 1.88 (0.77-4.55) Melancholic: <b>2.11 (1.04-4.29); p &lt; 0.05</b> Combined: 1.06 (0.34-3.32) Unspecified: 1.04 (0.57-1.92)	NR
Levitan 2012 (NESARC) (N = 6592)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for incident obesity; lifetime history assessed <sup>c</sup>	<u>Overall</u> Atypical: <b>2.61 (2.16-3.16); p &lt; 0.01</b> <u>Current MDD</u> Atypical: <b>3.22 (2.34-4.44); p &lt; 0.001</b> Undifferentiated: <b>1.38 (1.07-1.79); p &lt; 0.05</b> <u>Past MDD</u> Atypical: <b>2.38 (1.87-3.01); p &lt; 0.001</b>	NR
Mather 2009 (CCHS)	DSM-IV MDD criteria	OR (95% CI) for association between	<u>Lifetime MDD</u> Overall: <b>1.41 (1.22-1.64); p &lt; 0.001</b>	NR

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
(N = 34,900)	assessed using WMH-CIDI	obesity and depression; lifetime history assessed <sup>d</sup>	Men: <b>1.38 (1.05-1.81); p = 0.021</b> Women: <b>1.43 (1.21-1.68); p &lt; 0.001</b> <u>Past-year MDD</u> Overall: <b>1.24 (1.02-1.52); p = 0.034</b> Men: 1.21 (0.82-1.80); p = 0.337 Women: <b>1.27 (1.02-1.58); p = 0.035</b> Single MDD: 1.67 (0.64-4.29)	
Nigatu 2015 (PREVEND) (N = 1094)	DSM-IV MDD criteria assessed using CIDI 2.1	OR (95% CI) for baseline MDD and onset of obesity; mean 2.2-year follow-up <sup>e</sup>		Recurring MDD: 2.32 (0.82-6.58)
Patten 2009b (NPHS) (N = 11,502)	MDE criteria assessed using CIDI-SF	HR (95% CI) for incident obesity for participants with MDE; 10-year follow-up <sup>f</sup>	<u>Incident obesity<sup>g</sup></u> Diagnosis of MDE: 1.1 (0.8-1.5); p < 0.70 Use of venlafaxine: <b>4.9 (1.8-13.0); p &lt; 0.001</b> Use of SSRIs: <b>1.9 (1.2-3.2); p &lt; 0.01</b> <u>Risk of moving from nonobese to obese status</u> 0.6 (0.3-1.1); p = 0.11	NR
Polanka 2017 (NESARC) (N = 17,787)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for incidence of obesity in wave 2 according to depression at wave 1; mean 3-year follow-up <sup>h</sup>	<u>Non-atypical MDD</u> Overall: <b>1.11 (1.01-1.22); p &lt; 0.05</b> Non-Hispanic White: 1.09 (0.95-1.24) Non-Hispanic Black: 1.01 (0.87-1.17) Hispanic/Latino: <b>1.36 (1.21-1.53)</b> <u>Atypical MDD</u> Overall: <b>1.68 (1.43-1.97); p &lt; 0.001</b> Non-Hispanic White: <b>1.54 (1.25-1.91)</b> Non-Hispanic Black: <b>1.72 (1.31-2.26)</b> Hispanic/Latino: <b>1.97 (1.73-2.24)</b>	Dysthymic disorder only: <b>1.66 (1.29-2.12); p &lt; 0.001</b>
Vittengl 2018 (MIDUS) (N = 7108)	MDD criteria assessed using CIDI-SF	$\beta \pm$ SE path coefficients for relation between depression at time 1 and obesity at time 3; 18-year follow-up	<u>Mediation of depression effect on obesity</u> Physical impairment: <b>0.009 <math>\pm</math> 0.003; p &lt; 0.01</b> Social dysfunction: 0.002 $\pm$ 0.003 Emotional eating: <b>0.013 <math>\pm</math> 0.004; p &lt; 0.01</b>	NR
<b>Obesity as a component of metabolic syndrome</b>				
Block 2016 (SHIP-0; SHIP-TREND-0) (N = 8040)	DSM-IV MDD criteria assessed using CID-S or M-CIDI	OR (95% CI) for association between MDD and waist circumference $\geq$ 94 cm for males, $\geq$ 80 cm for	<u>Females</u> SHIP-0, depression at syndromal level: <b>0.71 (0.55-0.92); p <math>\leq</math> 0.05</b> SHIP-TREND-0 depression at syndromal level: 1.10 (0.89-1.35)	<u>Recurrent MDD</u> Females: <b>1.49 (1.12-1.97); p <math>\leq</math> 0.05</b> Males: 1.03 (0.72-1.47)

Study, N	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Presence of depression	Depression recurrence/severity
		females; 4-year follow-up <sup>i</sup>	MDD lifetime: 1.08 (0.85-1.38) <u>Males</u> SHIP-0, depression at syndromal level: 0.91 (0.64-1.31) SHIP-TREND-0 depression at syndromal level: 1.02 (0.79-1.32) MDD lifetime: 1.07 (0.80-1.44)	
Goldbacher 2009 (SWAN) (N = 429)	DSM-IV MDD criteria assessed using SCID-IV	HR (95% CI) for depression as a predictor of high waist circumference; 7-year follow-up <sup>j</sup>	1.47 (0.94-2.89)	NR
<b>Meta-analyses</b>				
de Wit 2010 (N = 204,507)	Diagnostic criteria (CIDI, DIS) and depression scales (CES-D, GDS)	Pooled OR (95% CI) for association between obesity and depression	All studies: <b>1.18 (1.01-1.37)</b> ; <b>p &lt; 0.01</b> Females: <b>1.32 (1.23-1.40)</b> ; <b>p ≤ 0.001</b> Males: 1.00 (0.76-1.31)	NR
Luppino 2010 (N = 58,745)	Clinical depression diagnosis or depressive symptoms	Pooled OR (95% CI) for depression exposure and overweight or obese status	<u>Obese/overweight</u> All adjusted: <b>1.40 (1.15-1.71)</b> ; <b>p &lt; 0.001</b> /0.98 (0.83-1.16); p = 0.81 Females: <b>2.01 (1.11-3.65)</b> / <b>1.11 (1.02-1.22)</b> Males: 1.43 (0.96-2.13)/1.07 (0.98-1.16) Age <20 years: <b>1.76 (1.42-2.18)</b> /1.43 (0.83-2.47) Age 20-60 years: 1.27 (0.88-1.82)/0.96 (0.81-1.41) Age >60 years: 1.40 (0.90-2.17)/NR	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for family history, parental characteristics, health investments, life shocks, proxies for risk tolerance, and use of prescription medications and antidepressants.

<sup>b</sup> Adjusted for age, sex, socioeconomic status, ethnicity, baseline BMI, length of follow-up, physical activity, smoking habit, alcohol use, substance dependence, living alone, anxiety disorders, antidepressant use, weight-increasing drug use, and presence of MDE during follow-up.

<sup>c</sup> Adjusted for age, sex, marital status, education, and employment.

<sup>d</sup> Adjusted for age, sex, education, and Charlson comorbidity index.

<sup>e</sup> Adjusted for age, sex, marital status, education, exercise, and smoking.

<sup>f</sup> Adjusted for age, sex, chronic conditions, low income.

<sup>g</sup> Unadjusted analysis; inclusion of covariates did not alter the association.

<sup>h</sup> Adjusted for age, sex, race/ethnicity, educational level, wave-1 BMI, lifetime alcohol use disorders, lifetime tobacco use, lifetime antidepressant use, cardiovascular disease, liver disease, arthritis, and study sampling design.

<sup>i</sup> Adjusted for age categories, marital status, education, employee status, smoking, physical inactivity, and risky alcohol consumption.

<sup>j</sup> Adjusted for baseline age and race.

AUDADIS, Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule; BMI, body mass index; CCHS, Canadian Community Health Survey-Mental Health and Well-Being; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; CIDI(-SF), Composite International Diagnostic Interview (Short Form); CID-S, Composite International Diagnostic-Screener; CoLaus/PsyCoLaus, Cohorte Lausannoise/Psychiatric arm of the CoLaus Study; DIGS, Diagnostic Interview for Genetic Studies; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Geriatric Depression Scale; HR, hazard ratio; M-CIDI, Munich-Composite International Diagnostic Interview; MDD, major depressive disorder; MDE, major depressive episode; MIDUS, Midlife Development in the United States Survey; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NPHS, National Population Health Survey; NR, not reported; OR, odds ratio; PREVEND, Prevention of Renal and Vascular End stage Diseases; SCID, Structured Clinical Interview for DSM-IV disorders; SE, standard error; SHIP, Study of Health In Pomerania; SSRI, selective serotonin reuptake inhibitor; SWAN, Study of Women's Health Across the Nation; WMH, World Mental Health.

### *Association Between Depression and Diabetes Severity*

The Hiles 2016 study (N = 2776) assessed abdominal obesity as an individual component of metabolic syndrome. Antidepressant use at year 0 was significantly associated with worsening of abdominal obesity at year 2 ( $\beta \pm SE: 1.2098 \pm 0.3120$ ;  $p < 0.001$ ), and antidepressant use at year 2 was also significantly associated with disease worsening at year 6 ( $\beta \pm SE: -1.4736 \pm 0.4298$ ;  $p = 0.001$ ). Similar significant associations were observed between IDS and disease severity over both time periods.

## Autoimmune, GI, and Musculoskeletal/Pain Conditions

### Autoimmune disorders

**Supplementary Table 27. Summary of studies assessing the association between depression and autoimmune disorder incidence**

Study, N	Depression definition	Estimate; time period	Disease/disorder	Impact of depression on comorbidity	
				Presence of depression	Depression recurrence/severity
Andersson 2015 (DCRS, DNHR, DPCRR) (N = 1,016,519)	ICD codes	IRR (95% CI) for risk of autoimmune diseases in patients with a history of depression; 17-year study period <sup>a</sup>	Any	Overall: <b>1.25 (1.19-1.31); p &lt; 0.01</b> 1 depressive episode only: <b>1.26 (1.19-1.33); p &lt; 0.01</b>	≥2 depressive episodes: <b>1.20 (1.05-1.38); p &lt; 0.01</b>
			Multiple sclerosis	Overall: <b>1.46 (1.26-1.69); p &lt; 0.01</b> 1 depressive episode only: <b>1.48 (1.27-1.74); p &lt; 0.01</b>	≥2 depressive episodes: 1.30 (0.88-1.92)
			SLE	Overall: <b>1.38 (1.00-1.91); p &lt; 0.01</b> 1 depressive episode only: 1.26 (0.89-1.78)	≥2 depressive episodes: <b>3.10 (1.16-8.26); p &lt; 0.01</b>
			Crohn disease	Overall: <b>1.36 (1.16-1.60); p &lt; 0.01</b> 1 depressive episode only: <b>1.37 (1.15-1.63); p &lt; 0.01</b>	≥2 depressive episodes: 1.31 (0.82-2.07)
			Ulcerative colitis	Overall: 1.17 (0.98-1.29) 1 depressive episode only: 1.13 (0.98-1.31)	≥2 depressive episodes: 1.02 (0.70-1.49)
			Celiac disease	Overall: 1.12 (0.81-1.53) 1 depressive episode only: 1.08 (0.76-1.53)	≥2 depressive episodes: 1.28 (0.59-2.80)
			Psoriasis	Overall: <b>1.45 (1.13-1.85); p &lt; 0.01</b> 1 depressive episode only: <b>1.46 (1.13-1.89); p &lt; 0.01</b>	≥2 depressive episodes: 1.53 (0.72-3.26)
			Rheumatoid arthritis	Overall: 1.01 (0.90-1.44) 1 depressive episode only: 1.06 (0.93-1.20)	≥2 depressive episodes: 0.80 (0.57-1.12)
			Ankylosing spondylitis	Overall: 1.14 (0.85-1.53) 1 depressive episode only: 1.09 (0.79-1.49)	≥2 depressive episodes: 1.60 (0.70-3.67)
Farmer 2008 (N = 2430)	DSM-IV or ICD recurrent MDD	OR (95% CI) for cases with depression vs.	Rheumatoid arthritis	NR	Recurrent: 2.72 (1.31-5.63); p = 0.10 <sup>c</sup>

Study, N	Depression definition	Estimate; time period	Disease/disorder	Impact of depression on comorbidity	
				Presence of depression	Depression recurrence/severity
	criteria assessed using SCAN 2.1	controls; lifetime history assessed <sup>b</sup>			
Johansson 2014 (Swedish NPR) (N = 1,897,269)	ICD codes	HR (95% CI) for incident disease according to depression <sup>d</sup>	Multiple sclerosis	Overall: <b>1.86 (1.73-2.00); p &lt; 0.001</b> Male: <b>2.20 (1.90-2.54); p &lt; 0.0001</b> Female: <b>1.77 (1.63-1.92); p &lt; 0.0001</b>	<u>Severe depression only</u> Overall: <b>1.46 (1.27-1.68); p &lt; 0.0001</b> Male: <b>1.84 (1.40-2.44); p &lt; 0.0001</b> Female: <b>1.36 (1.15-1.60); p = 0.0003</b>
Nicholl 2008 (N = 2456)	HADS ≥10 <sup>e</sup>	OR (95% CI) for IBS by baseline HADS; 15-month follow-up <sup>f</sup>	IBS	NR	<u>By HADS cutoff</u> 0-2: reference 3-5: 0.83 (0.4-1.6) 6-21: 0.73 (0.4-1.5)
Patten 2008 (NPHS) (N = 15,254)	DSM-IV MDD criteria assessed using CIDI-SF	HR (95% CI) for incident disease according to MDD; 8-year study period with 2-year assessments <sup>g</sup>	Arthritis/rheumatism	MDD at baseline interview: <b>1.7 (1.3-2.2)</b> MDD as a time-varying characteristic: 1.3 (1.0-1.7)	<u>By duration of past-year MDD episode<sup>h</sup></u> 2-12 weeks: 1.2 (0.8-1.7) 13-52+ weeks: <b>2.2 (1.5-3.3)</b>
Vallerand 2018 (THIN database) (N = 5,743,331)	Diagnostic Read codes	HR (95% CI) for incident disease according to the presence of depression; median 6.7-year follow-up <sup>i</sup>	Rheumatoid arthritis	<b>1.38 (1.31-1.46); p &lt; 0.0001</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, and psychiatric comorbidities.

<sup>b</sup> Adjusted for age, sex, BMI, and multiple testing.

<sup>c</sup> Study examines lifetime prevalence of comorbidities; unclear if these were determined to have occurred after MDD episodes.

<sup>d</sup> Results are not adjusted, however, authors report that adjustment for immigration status did not change results (data NR).

<sup>e</sup> Methods state 10-11 for a high probability of a depression disorder; however, analysis uses a cutoff of 6.

<sup>f</sup> Adjusted for age, sex, and baseline abdominal pain status.

<sup>g</sup> Adjusted for age, sex, and ≥2 physician visits during preceding year.

<sup>h</sup> Unadjusted.

<sup>i</sup> Adjusted for age (as a continuous variable), sex, smoking status, BMI, Charlson Comorbidity index, and antidepressant use.

BMI, body mass index; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; DCRS, Danish Civil Registration System; DNHR, Danish National Hospital Register; DPCRR, Danish Psychiatric Central Research Register; DSM, Diagnostic and Statistical Manual of Mental Disorders; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; IBS, irritable bowel syndrome; ICD, International Classification of Diseases; IRR, incident rate

ratio; MDD, major depressive disorder; NPHS, National Population Health Survey; NPR, National Population Register; NR, not reported; OR, odds ratio; SCAN, Schedules for the Clinical Assessment of Neuropsychiatry; THIN, The Health Improvement Network.

#### *Association Between Depression and Autoimmune Disorder Severity*

No studies were identified by the SLR for this association.

#### *Association Between Depression and Multiple Sclerosis Severity*

No studies were identified by the SLR for this association.

#### *Association Between Depression and Rheumatoid Arthritis Severity*

In patients with arthritis and other rheumatic conditions, MDD was shown to be significantly associated with arthritis-attributable occupational disability (OR 1.48; 95% CI: 1.03-2.13), although it did not impact self-reported limitations in either social activities or general activities [Delgado 2019; N = 29,886].

#### *Association Between Depression and Crohn Disease Severity*

Persoons 2005 (N = 100) explored the impact of depression on the response to infliximab treatment, demonstrating a significant association between MDD at baseline and failure to achieve Crohn disease remission at 4 weeks (OR 0.166; 95% CI: 0.049-0.567; p = 0.004) as well as a faster time to Crohn disease retreatment (HR 2.271; 95% CI: 1.36-3.79; p = 0.002). Patients with persistent MDD that was present at both baseline and 4 weeks were also shown to have a greater risk of earlier Crohn disease relapse (RR 3.218; 95% CI: 1.712-6.051; p < 0.001).

#### *Association Between Depression and SLE, Ankylosing Spondylitis, Psoriasis, Ulcerative Colitis, and Celiac Disease Severity*

No studies were identified by the SLR for this association.



Pain conditions

**Supplementary Table 28. Summary of studies assessing the association between depression and musculoskeletal condition and pain incidence**

Study, N	Depression definition	Estimate; time period	Disease/disorder	Impact of depression on comorbidity	
				Presence of depression	Depression recurrence/severity
<b><i>Migraine or headache</i></b>					
Modgill 2012, Swanson 2013 (NPHS) <sup>a</sup> (N = 15,254)	DSM-IV MDE criteria assessed using CIDI-SF	HR (95% CI) of MDE as risk factor for migraine; 14-year follow-up <sup>b</sup>	Migraine	Modgill 2012 analysis: 0.9 (0.6-1.2); p = 0.595 <sup>c</sup> Swanson 2013 analysis: 1.30 (0.80-2.10)	NR
Pisanu 2019 (CoLaus/PsyCoLaus) (N = 2957)	DSM-IV MDD criteria assessed using DIGS	OR for lifetime MDD subtypes and any migraine <sup>d</sup>	Migraine <sup>e</sup>	<u>Any migraine</u> Atypical MDD: 0.93; p = 0.882 Combined MDD: 0.82; p = 0.781 <u>Migraine without/with aura</u> MDD: 0.70; p = 0.214/ <b>3.18; p = 0.004</b> Melancholic MDD: 0.81; p = 0.588/ <b>3.32; p = 0.038</b> Unspecified MDD: 0.54; p = 0.080/ <b>3.75; p = 0.012</b>	NR
Samaan 2009 <sup>f</sup> (N = 2110)	DSM-IV or ICD recurrent MDD criteria assessed using SCAN 2.1	OR (95% CI) for cases with recurrent depression vs. controls; lifetime history assessed <sup>g</sup>	Migraine and headache <sup>h</sup>	NR	<u>Recurrent MDD</u> Migraine with aura: <b>5.6 (3.54-9.0); p &lt; 0.0001<sup>i</sup></b> Migraine without aura: <b>3.7 (2.2-6.14); p &lt; 0.0001</b> Probable migraine: <b>3.6 (2.7-5.0); p &lt; 0.0001</b> Non-migraine headache: <b>2.6 (2.0-3.2); p &lt; 0.0001</b>
<b><i>Other pain conditions</i></b>					
Linton 2005 (N = 1914)	HADS; specific criteria NR	OR (95% CI) for development of significant pain problem; 1-year follow-up <sup>g</sup>	Spinal pain	NR	Based on HADS median split: 1.29 (0.54-3.09); p = 0.5677 <sup>i</sup>
Pinheiro 2015 (N = 28,326)	Any method of depression	Pooled OR (95% CI) for new episodes of low back pain	Low back pain	<b>1.59 (1.26-2.01)</b>	<u>In studies that provided symptom-stratified data</u>

Study, N	Depression definition	Estimate; time period	Disease/disorder	Impact of depression on comorbidity	
				Presence of depression	Depression recurrence/severity
	assessment included				Most severe level of depression: <b>2.51 (1.58-3.99)</b> Lowest level of depression: 1.51 (0.89-2.56) NR
Velly 2011 (N = 480)	BDI classified as mild (14-19), moderate (20-28), severe (29-63)	OR (95% CI) for the onset of clinically significant pain; 18-month follow-up <sup>k</sup>	TMJ pain	1.34 (0.82-2.18); p = 0.25	NR
<b>Arthritis and osteoporosis</b>					
Farmer 2008 <sup>f</sup> (N = 2430)	DSM-IV or ICD recurrent MDD criteria assessed using SCAN 2.1	OR (95% CI) for cases with depression vs. controls; lifetime history assessed <sup>l</sup>	Osteoarthritis Osteoporosis	NR NR	Recurrent: <b>3.05 (1.83-5.08); p = 0.00042<sup>h</sup></b> Recurrent: 3.35 (1.38-8.13); p = 0.11 <sup>h</sup>
Karakus 2011 (Health and Retirement Study) (N = 3645)	8-item CES-D ≥3	OR (95% CI) for incident arthritis according to depression at baseline; 12-year follow-up	Arthritis	<b>1.50 (1.09-2.05); p = 0.01</b>	NR
<b>Multiple disorders</b>					
Patten 2008 (NPHS) <sup>a</sup> (N = 15,254)	DSM-IV MDD criteria assessed using CIDI-SF	HR (95% CI) for incident disease in according to MDD; 8-year study period with 2-year assessments <sup>m</sup>	Migraine Back problems	MDD at baseline interview: 1.4 (0.7-2.9) MDD as a time-varying characteristic: <b>2.1 (1.2-3.6)<sup>n</sup></b> MDD at baseline interview: <b>1.4 (1.1-1.7)</b> MDD as a time-varying characteristic: <b>1.3 (1.1-1.6)</b>	<u>By duration of past-year MDD episode<sup>o</sup></u> 2-12 weeks: 1.7 (0.7-3.8) 13-52+ weeks: 1.8 (0.4-7.8) <u>By duration of past-year MDD episode<sup>o</sup></u> 2-12 weeks: 1.3 (1.0-1.7) 13-52+ weeks: 1.5 (1.0-2.1)

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> The NPHS dataset was used to assess migraine incidence in Modgill 2012, Swanson 2013, and Patten 2008; the Patten study examined an 8-year follow-up whereas Modgill and Swanson examined a 14-year follow-up.

<sup>b</sup> Adjusted for age, sex, stress, and childhood trauma; Swanson provides detailed stepwise adjustment for recent marital status change, recent unemployment,

work stress, chronic stress, change in social support; unclear how much this differed from adjustments made in Modgill analysis.

<sup>c</sup> Analysis significant a lower levels of adjustment only.

<sup>d</sup> Adjusted for age, sex, and socioeconomic status.

<sup>e</sup> Lifetime MDD and lifetime migraine were assessed, no clear directionality.

<sup>f</sup> Farmer 2008 and Samaan 2009 analyzed the same dataset, numbers of cases and controls differed slightly (1546 cases, 888 controls for Farmer; 1259 cases, 851 controls for Samaan; unclear to what extent these participants overlapped).

<sup>g</sup> Adjustment unclear.

<sup>h</sup> Study examines lifetime prevalence of comorbidities; unclear if these were determined to have occurred after MDD episodes; p-value corrected for multiple testing.

<sup>i</sup> When recurrent headache excluded, only migraine with aura remained significant.

<sup>j</sup> Median NR, thus severity of depression unclear.

<sup>k</sup> Adjusted for age, sex, catastrophizing, pain intensity at baseline, and widespread pain.

<sup>l</sup> Adjusted for age, sex, and BMI.

<sup>m</sup> Adjusted for age, sex, and  $\geq 2$  physician visits during preceding year.

<sup>n</sup> Only patients aged  $< 26$  were analyzed as age-by-MDD interaction was observed in preliminary analyses to be present only in this age group.

<sup>o</sup> Unadjusted.

BDI, Beck Depression Inventory; BMI, body mass index; CES-D, Center for Epidemiological Studies-Depression; CI, confidence interval; CIDI-SF, Composite International Diagnostic Interview Short Form; CoLaus/PsyCoLaus, Cohorte Lausannoise/Psychiatric arm of the CoLaus Study; DIGS, Diagnostic Interview for Genetic Studies; DSM, Diagnostic and Statistical Manual of Mental Disorders; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; ICD, International Classification of Diseases; MDD, major depressive disorder; MDE, major depressive episode; NPHS, National Population Health Survey; NR, not reported; OR, odds ratio; SCAN, Schedules for the Clinical Assessment of Neuropsychiatry; TMJ, temporomandibular joint.

**Supplementary Table 29. Summary of studies assessing the association between depression and pain severity**

Study, N	Depression definition	Estimate; time period	Disease/disorder	Impact of depression on comorbidity	
				Presence of depression	Depression severity
<b><i>Migraine or headache</i></b>					
Pisanu 2019 (CoLaus/PsyCoLaus) (N = 2957)	DSM-IV MDD criteria assessed using DIGS	$\beta$ for linear regression of lifetime MDD subtypes and migraine frequency <sup>a</sup>	Migraine	<u>Migraine frequency</u> Lifetime MDD: 0.09; p = 0.053 Atypical MDD: 0.03; p = 0.558 Combined MDD: <b>0.12; p = 0.019</b> Unspecified MDD: 0.07; p = 0.194	NR
Tietjen 2007 (N = 721)	PHQ-9 $\geq 10$ for current depression, $\geq 15$ for MDD	OR (95% CI) for frequency and disability <sup>b</sup>	Migraine	<u>Among patients with current depression vs. normal BMI/no depression</u> <u>Migraine frequency</u> Normal BMI: <b>2.63 (1.46-4.75); p &lt; 0.01</b> Overweight: <b>3.26 (1.53-6.91); p &lt; 0.01</b> Obese: <b>4.16 (1.92-8.99), p &lt; 0.001</b>	NR

Study, N	Depression definition	Estimate; time period	Disease/disorder	Impact of depression on comorbidity	
				Presence of depression	Depression severity
				<i>Migraine disability</i> Normal BMI: <b>4.19 (1.51-11.63)</b> ; <b>p &lt; 0.01</b> Overweight: <b>6.68 (2.45 to 18.26)</b> ; <b>p &lt; 0.001</b> Obese: <b>7.10 (2.69-18.77)</b> ; <b>p &lt; 0.001</b>	
<b><i>Other pain conditions</i></b>					
Begre 2008 (N = 505)	Physician diagnosis	Correlations between pain measures and CGI scores at study baseline <sup>c</sup>	Total pain	NR	Prior to treatment: CGI score and total pain severity were correlated ( <b>r = 0.32, p &lt; 0.001</b> ) Total pain severity correlated with duration of depressive symptoms ( <b>r = 0.09, p = 0.037</b> ) <u>Mild/moderate vs. no pain<sup>e</sup></u> Moderately depressed: 3.8 (0.7-21.0) Severely depressed: 3.3 (0.6-17.7) <u>Severe pain vs. no pain<sup>e</sup></u> Moderately depressed: 1.3 (0.3-4.7) Severely depressed: 2.0 (0.6-6.7)
Ohayon 2010 (N = 3243)	48-item questionnaire	OR (95% CI) by depression severity status for severity of pain vs. no depression <sup>d</sup>	Chronic pain	NR	
Ryall 2007 (N = 267)	HADS ≥8	OR (95% CI) for prevalence of pain at 12 months <sup>f</sup>	Arm pain	Continuing pain: 1.4 (0.8-2.4) Frequent continuing pain: 1.6 (0.8-3.3) Unremitting pain: 1.3 (0.7-2.4)	NR
Velly 2011 (N = 480)	BDI classified as mild (14-19), moderate (20-28), severe (29-63)	β (95% CI) for contribution of baseline depression to increase in pain intensity/disability score <sup>g</sup>	TMJ pain	Pain intensity: 1.10 (0.81-3.00); p = 0.26 <sup>h</sup> Disability: <b>0.50 (0.37-0.63)</b> ; <b>p &lt; 0.0001</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences (p < 0.05) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, sex, and socioeconomic status.

<sup>b</sup> Adjusted for age, sex, ethnicity, education, household income, and antidepressant or anxiolytic medication use.

<sup>c</sup> Unadjusted.

<sup>d</sup> Adjusted for age and sex.

<sup>e</sup> Sequence of pain and depressive episodes showed that in over half of cases (57.1%) pain appeared before the depressive episode; the sequence data were not accounted for in the severity association analysis.

<sup>f</sup> Adjusted for age, sex, diagnostic group at baseline, frequency/severity of pain at baseline, and source from which the patient was recruited; depression not added to step-wise regression analysis of risk factors for continuing pain.

<sup>g</sup> Adjusted for age, sex, catastrophizing, pain intensity or disability score at baseline, and widespread pain.

<sup>h</sup> Analysis significant at lower levels of adjustment only.

BDI, Beck Depression Inventory; BMI, body mass index; CGI, Clinical Global Impression; CI, confidence interval; CoLaus/PsyCoLaus, Cohorte Lausannoise/Psychiatric arm of the CoLaus Study; DIGS, Diagnostic Interview for Genetic Studies; DSM, Diagnostic and Statistical Manual of Mental Disorders; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; MDD, major depressive disorder; NR, not reported; OR, odds ratio; PHQ, Patient Health Questionnaire; TMJ, temporomandibular joint.

## GI ulcers

### *Association Between Depression and Risk of Incident GI Ulcers*

Both Farmer 2008 (N = 2430) and Patten 2008 (N = 15,254) assessed the relationship between depression and gastric ulcers. Both studies reported significant associations between depression and incident ulcers, although directionality was unclear in the Farmer 2008 study where all patients had recurrent depression (OR 4.31; 95% CI: 1.94-9.57; p = 0.0047). In Patten 2008, both MDD at baseline (HR 1.5; 95% CI: 1.0-2.2) and as a time-varying characteristic (HR 1.8; 95% CI: 1.2-2.8) was associated with incidence of peptic ulcers.

### *Association Between Depression and GI Ulcer Severity*

No studies were identified by the SLR for this association.

## Substance abuse disorders

**Supplementary Table 30. Summary of studies assessing the association between depression and substance use disorder incidence**

Study, N	Depression definition	Estimate; time period	Substance(s)	Impact of depression on comorbidity	
				Presence of depression	Depression severity
<b><i>Alcohol abuse only</i></b>					
Baggio 2015 (C-SURF) (N = 4352)	DSM-IV MDD criteria assessed using MDI	Effect estimate for later alcohol use disorder according to MDD at baseline; mean 15-month follow-up <sup>a</sup>	Alcohol	$\beta = 0.017$ ; $p = 0.839$	NR
Briere 2014 (Oregon Adolescent Depression Project) (N = 816)	DSM-III-R MDD criteria <sup>b</sup>	Effect estimate for later alcohol use disorder; 6-year follow-up <sup>c</sup>	Alcohol	<u>MDD assessed age 24, alcohol use assessed age 30</u> $\beta = 0.15$ ; $p < 0.05$	NR
Bulloch 2012 (NPHS) (N = 15,254)	DSM-IV MDE criteria assessed using CIDI-SF	HR (95% CI) according to MDE at baseline; 12-year follow-up <sup>d</sup>	Alcohol <sup>e</sup>	Alcohol dependence: 1.6 (0.5-5.2); $p = 0.44$ Excessive alcohol consumption: 1.1 (0.8-1.5); $p = 0.74$	NR
Kuo 2006 (Virginia Twin Registry) (N = 7477)	DSM-III-R MDD criteria assessed using SCID	HR (95% CI) for alcohol dependency in patients with prior MDD; lifetime history assessed <sup>f</sup>	Alcohol	Lifetime MDD: <b>1.31 (1.02-1.67)</b> ; $p < 0.05$ Concurrent MDD: <b>2.36 (1.51-3.68)</b> ; $p < 0.001$ MDD as a time-dependent variable: <b>3.87 (2.30-6.52)</b> ; $p < 0.001$	NR
McCarty 2009 (N = 776)	DSM-IV MDD criteria assessed using modified DIS	OR (95% CI) for alcohol use disorder; 6-year follow-up <sup>g</sup>	Alcohol	<u>MDE assessed age 24, alcohol use assessed age 27</u> Women: NS Men: NS <u>MDE assessed age 27, alcohol use assessed age 30</u> Women: <b>3.11 (1.29-7.54)</b> Men: NS	NR
Melartin 2014 (Vantaa)	DSM-IV MDD criteria	Latent curve model predicting alcohol use	Alcohol	NR	BDI score at baseline: <b>0.47</b> ; $p < 0.01$

Study, N	Depression definition	Estimate; time period	Substance(s)	Impact of depression on comorbidity	
				Presence of depression	Depression severity
Depression Study) (N = 193)	assessed using SCAN 2.0	disorder at month 6 according to depression at baseline			
<b><i>Drug abuse only</i></b>					
Dunn 2018 (NSDUH) (N = 261.19 million)	NR	OR (95% CI) of misusing other prescription drugs compared with individuals who do not use stimulants <sup>h</sup>	Prescription drug misuse	<u>Respondents with/without a history of MDE</u> Appropriate users of stimulants: <b>2.19; p &lt; 0.001/1.35; p &lt; 0.0001</b> Misusers of stimulants: <b>18.67; p &lt; 0.001/8.65; p &lt; 0.0001</b>	NR
Grant 2016 (NESARC-III) (N = 36,309)	DSM-V MDD criteria assessed using AUDADIS-V	OR (95% CI) of prevalence of drug use disorder in patients with MDD; 2- year study period assessing lifetime history <sup>i</sup>	Drug use disorder	12-month drug-use disorder: <b>1.3 (1.09-1.64); p &lt; 0.05</b> Lifetime drug use disorder: <b>1.2 (1.01-1.32); p &lt; 0.05</b>	NR
Inguva 2018 (N = 1364)	NR	OR (95% CI) for depression as a predictor of overdose; depression assessed 6 months prior to overdose	Opioid overdose	<b>4.8 (2.87-8.29)</b>	NR
Martins 2009 (NESARC) (N = 43,093)	DSM-IV MDD criteria assessed using AUDADIS-IV	HR (95% CI) of opioid use according to pre-existing MDD; lifetime history assessed <sup>d</sup>	Non-medical opioid use	Non-medical opioid use: <b>2.8 (2.4-3.4); p &lt; 0.001</b> Opioid dependence from non-medical use: <b>4.6 (2.8-7.6); p &lt; 0.001</b>	NR
Martins 2012 (NESARC) (N = 34,653)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for incident non-medical opioid use or abuse according to lifetime MDD at baseline; 3-year follow-up <sup>k</sup>	Non-medical opioid use	Non-medical opioid use: <b>1.5 (1.2-2.8); p &lt; 0.01</b> Opioid dependence from non-medical use: <b>1.7 (1.2-2.5); p &lt; 0.01</b>	NR
Shi 2014 (NSDUH) (N = 39,133)	DSM-IV MDE criteria assessed using CIDI	OR (95% CI) for marijuana use according to lifetime depression diagnosis <sup>l</sup>	Marijuana use	<u>Frequent use</u> Past MDE: 1.24 (0.99-1.55); p < 0.05 Recent MDE: <b>1.54 (1.24-1.91); p &lt; 0.001</b> <u>Dependence or abuse</u>	NR

Study, N	Depression definition	Estimate; time period	Substance(s)	Impact of depression on comorbidity	
				Presence of depression	Depression severity
				Past MDE: <b>1.52 (1.01-2.26); p &lt; 0.05</b> Recent MDE: <b>2.97 (2.30-3.85); p &lt; 0.001</b>	
Sintov 2009 (IASPSAD) (N = 855)	DSM-IV MDD criteria assessed using SCID	OR (95% CI) for primary depression as a predictor for drug dependence; lifetime history assessed <sup>m</sup>	Any drug	<b>11.84 (6.00-23.35); p &lt; 0.0001</b>	NR
			Cannabis	<b>5.14 (1.92-13.73); p = 0.0011</b>	NR
			Sedative	<b>12.40 (4.96-31.04); p &lt; 0.0001</b>	NR
			Stimulant	<b>6.77 (1.33-34.50); p = 0.02</b>	NR
			Cocaine	1.35 (0.60-3.06); p = 0.46	NR
			Opioid	<b>2.38 (1.24-4.55); p = 0.009</b>	NR
			Hallucinogen	2.45 (0.88-6.76); p = 0.09	NR
<b><i>Both drug and alcohol abuse</i></b>					
Brenner 2018 (N = 121,669)	NR for MDD; treatment resistant: received ≥3 treatment episodes within a single depressive episode	HR (95% CI) for substance use disorder for treatment-resistant depression vs. MDD; mean 4.2-year follow-up <sup>n</sup>	Any	NR	<b>1.6 (1.5-1.7)</b>
			Alcohol	NR	<b>1.2 (1.1-1.3)</b>
			Opioids	NR	<b>2.1 (1.7-2.6)</b>
			Sedatives	NR	<b>2.8 (2.4-3.3)</b>
			Multiple drug use	NR	<b>2.3 (2.0-2.6)</b>
Leventhal 2008 (Oregon Adolescent Depression Project) (N = 460)	DSM-IV MDD criteria <sup>b</sup>	OR (95% CI) for melancholic MDD status on subsequent abuse/dependence; 6-year follow-up <sup>o</sup>	Alcohol abuse/dependence	1.56 (0.58-4.22)	NR
			Stimulant abuse/dependence	<b>4.46 (1.07-18.59); p &lt; 0.05</b>	NR
			Cannabis abuse/dependence	3.65 (0.78-17.04)	NR
			High-quantity alcohol use	<u>Diagnosis of depression</u> Women: <b>1.23 (0.99-1.52); p &lt; 0.05</b> Men: 1.30 (0.99-1.70); p < 0.05 <u>Taking antidepressants prior to current wave</u> Women: 0.94 (0.62-1.42) Men: 0.56 (0.25-1.27)	NR
Lo 2015 (FFCW) (N = 5573)	Depression assessed using CIDI	OR (95% CI) for alcohol/drug abuse in the past year according to depression prior to current wave; 11-year follow-up in 2-year waves <sup>p</sup>	Illicit drug use	<u>Diagnosis of depression</u> Women: <b>1.48 (1.13-1.95); p &lt; 0.01</b>	NR



Study, N	Depression definition	Estimate; time period	Substance(s)	Impact of depression on comorbidity	
				Presence of depression	Depression severity
				Men: 1.12 (0.79-1.59) <u>Taking antidepressants prior to current wave</u> Women: 0.86 (0.51-1.45) Men: 0.54 (0.22-1.35)	
Merikangas 2008 (Zurich Cohort Study) (N = 591)	DSM-IV MDD criteria assessed using SPIKE	OR (95% CI) for subsequent abuse of alcohol or drugs <sup>a</sup>	Alcohol abuse/dependence Cannabis	Abuse: 1.8 (0.6-2.9) Dependence: 2.2 (0.7-7.2) Use: 1.5 (0.7-3.6) Abuse/dependence: 2.3 (0.7-6.9) Use: 2.7 (0.7-10.2) Abuse/dependence: <b>13.2 (2.6-67.7)</b>	NR NR NR
Olfson 2017 (NESARC) (N = 34,653)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for wave 2 past-year disorders among adults with vs. without past-year MDE at wave 1; waves 3 years apart <sup>f</sup>	Alcohol use disorder Drug use disorder	Any alcohol use disorder: 1.04 (0.85-1.27) Alcohol abuse: 0.93 (0.75-1.16) Alcohol dependence: 1.19 (0.91-1.56) Any drug use disorder: 1.17 (0.85-1.59) Drug abuse: 1.19 (0.81-1.75) Drug dependence: 1.34 (0.83-2.18)	NR NR
Pacek 2013 (NESARC) (N = 3320)	DSM-IV MDD criteria assessed using AUDADIS-IV	OR (95% CI) for lifetime depression and incident use disorders; 3-year follow-up <sup>g</sup>	Alcohol use disorder Cannabis use disorder Both alcohol and cannabis use disorder	Alcohol use disorder: 1.04 (0.82-1.32) Alcohol abuse: 0.76 (0.56-1.02) Alcohol dependence: <b>1.47 (1.06-2.03); p &lt; 0.05</b> Cannabis use disorder: <b>2.28 (1.28-4.05); p &lt; 0.05</b> Cannabis abuse: <b>2.96 (1.55-5.65); p &lt; 0.05</b> Cannabis dependence: 0.77 (0.22-2.64) Alcohol use disorder + cannabis use disorder: 1.51 (0.70-3.23) Alcohol dependence + cannabis dependence: <b>4.51 (1.31-15.60); p &lt; 0.05</b>	NR NR NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported

where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for age, alcohol use at baseline, education, financial situation, age of onset of alcohol use, risky single-occasion drinking, and language.

<sup>b</sup> Assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (wave 1); Longitudinal Interval Follow-up Evaluation (subsequent waves).

<sup>c</sup> Adjusted for anxiety disorders, disruptive behavior disorders, and other substance use disorders in adolescence.

<sup>d</sup> Adjusted for age, sex, chronic conditions, pain, and smoking.

<sup>e</sup> Alcohol dependence measured using a logistic model; excessive alcohol consumption measured using a proportional hazards model.

<sup>f</sup> Controlled for familial shared liability of alcohol dependency and MDD.

<sup>g</sup> Controlled for the effects of income at age 24.

<sup>h</sup> Adjusted for covariates, details NR.

<sup>i</sup> Directionality unclear for this analysis; adjusted for age, sex, ethnicity, education, family income, marital status, urbanicity, geographic region, and additional psychiatric comorbidity.

<sup>j</sup> Adjusted for sex, ethnicity, income, education, and employment status.

<sup>k</sup> Adjusted for demographics, comorbid mood and anxiety disorders, and other substance use.

<sup>l</sup> Adjusted for age, sex, marital status, ethnicity, educational attainment, employment status, poverty level, and perceived health status.

<sup>m</sup> Models included age, sex, education, neuroticism, novelty seeking, conduct disorder, nicotine dependence, age of onset of alcohol use, early drug use, maternal alcohol dependence, and paternal alcohol dependence; models adjusted for different factors for each outcome based on whether they reached significance in initial block models.

<sup>n</sup> Adjusted for age, sex, area of residence, education level, anxiety disorders, and personality disorders.

<sup>o</sup> MDD assessed age 24, alcohol use assessed age 30; adjusted for age; sex; wave 3 lifetime histories of anxiety disorders, disruptive behavior disorders, and cigarette smoking; age of first onset MDD, and number of previous MDD episodes; total duration of previous MDD episodes, and severity of worst MDD episode by wave 3.

<sup>p</sup> Adjusted for age, ethnicity, employment, income:poverty ratio, marital status, and education level.

<sup>q</sup> Adjusted for sex and time in study.

<sup>r</sup> Adjusted for age, sex, ethnicity, marital status, employment, education, mental component summary score, physical component summary score, and each of the lifetime psychiatric disorders at wave 1.

<sup>s</sup> Adjusted for age, sex, marital status, ethnicity, income, education, and other drug use disorders.

AUDADIS, Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule; BDI, Beck Depression Inventory; CI, confidence interval; CIDI(-SF), Composite International Diagnostic Interview (Short Form); C-SURF, Cohort Study on Substance Use Risk Factors; DIS, Diagnostic Interview Schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; FFCW, Fragile Families and Child Wellbeing study; HR, hazard ratio; IASPSAD, Irish Affected Sib Pair Study of Alcohol Dependence; MDD, major depressive disorder; MDE, major depressive episode; MDI, Major Depression Inventory; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NPHS, National Population Health Survey; NR, not reported; NS, not significant; NSDUH, National Survey on Drug Use and Health; OR, odds ratio; SCAN, Schedules for the Clinical Assessment of Neuropsychiatry; SCID, Structured Clinical Interview for DSM-IV disorders; SPIKE, Structured Diagnostic Interview for Psychopathologic and Somatic Syndromes.

**Supplementary Table 31. Summary of studies assessing the association between depression and substance use disorder severity**

Study	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Depression prevalence	Depression severity
<b>Severity of alcohol abuse</b>				
Baggio 2015 (C-SURF) (N = 4352)	DSM-IV MDD criteria assessed using MDI	Effect estimate for cross-sectional association between MDD and alcohol use disorder <sup>a</sup>	Depressive participants reported a higher number of alcohol use disorder symptoms ( $\beta = 0.743$ ; $p < 0.001$ ) The interaction between MDD and alcohol use was negative ( $\beta = -0.204$ ; $p = 0.001$ )	NR
Briere 2014 (Oregon Adolescent Depression Project) (N = 816)	DSM-III-R MDD criteria <sup>b</sup>	Effect estimate or OR (95% CI) for impact of MDD on alcohol use disorder severity and duration <sup>c</sup>	<u>Alcohol use disorder severity</u> MDD + alcohol use disorder vs. alcohol use disorder only: OR <b>2.6 (1.5-4.6)</b> ; $p < 0.001$ <u>Alcohol use disorder duration</u> MDD + alcohol use disorder vs. alcohol use disorder only: $\beta = -16.7 (-57.0-23.6)$	NR
Karpyak 2019 (N = 443)	DSM-IV MDD criteria assessed using PRISM	Effect estimate $\pm$ SE for association of alcohol consumption measures with MDD; lifetime history assessed	<u>Comorbid lifetime MDD/current MDD</u> Total drinks: $-0.2000 \pm 0.111$ ; $p = 0.072/0.0597 \pm 0.167$ ; $p = 0.72$ No. days drinking: <b><math>-0.2225 \pm 0.111</math></b> ; $p = 0.045$ / $-0.1409 \pm 0.167$ ; $p = 0.40$ No. heavy drinking days: <b><math>-0.2242 \pm 0.110</math></b> ; $p = 0.042$ / $-0.0609 \pm 0.166$ ; $p = 0.71$ Mean drinks per drinking day: $-0.0622 \pm 0.033$ ; $p = 0.57/0.2789 \pm 0.165$ ; $p = 0.091$ Max. drinks per drinking day: $-0.0537 \pm 0.111$ ; $p = 0.63/0.2190 \pm 0.165$ ; $p = 0.19$ <i>Males only</i> Total drinks: $-0.2621 \pm 0.157$ ; $p = 0.096$ / $-0.0708 \pm 0.217$ ; $p = 0.74$ No. days drinking: <b><math>-0.4094 \pm 0.154</math></b> ; $p = 0.0084$ / $-0.2912 \pm 0.215$ ; $p = 0.18$ No. heavy drinking days: <b><math>-0.3591 \pm 0.155</math></b> ; $p = 0.021$ / $-0.2213 \pm 0.216$ ; $p = 0.31$ Mean drinks per drinking day: $-0.0321 \pm 0.153$ ; $p = 0.83/0.1987 \pm 0.210$ ; $p = 0.34$	<u>According to PHQ-9 severity</u> Total drinks: $0.0149 \pm 0.008$ ; $p = 0.057$ No. days drinking: $0.0127 \pm 0.008$ ; $p = 0.10$ No. heavy drinking days: $0.0142 \pm 0.008$ ; $p = 0.067$ Mean drinks per drinking day: $0.0130 \pm 0.008$ ; $p = 0.094$ Max. drinks per drinking day: $0.0106 \pm 0.008$ ; $p = 0.17$ <i>Males only</i> Total drinks: $0.0125 \pm 0.010$ ; $p = 0.21$ No. days drinking: $0.0098 \pm 0.010$ ; $p = 0.32$ No. heavy drinking days: $0.0106 \pm 0.010$ ; $p = 0.28$ Mean drinks per drinking day: $0.0113 \pm 0.010$ ; $p = 0.24$ Max. drinks per drinking day: $0.0095 \pm 0.010$ ; $p = 0.33$ <i>Females only</i> Total drinks: $0.0211 \pm 0.012$ ; $p = 0.073$ No. days drinking: $0.0185 \pm 0.012$ ; $p = 0.14$

Study	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Depression prevalence	Depression severity
			Max. drinks per drinking day: $-0.0819 \pm 0.154$ ; $p = 0.59/0.0674 \pm 0.212$ ; $p = 0.75$ <i>Females only</i> Total drinks: $0.0211 \pm 0.149$ ; $p = 0.89/0.0962 \pm 0.200$ ; $p = 0.63$ No. days drinking: $0.0250 \pm 0.159$ ; $p = 0.88/-0.0406 \pm 0.214$ ; $p = 0.85$ No. heavy drinking days: $-0.0270 \pm 0.155$ ; $p = 0.86/0.0138 \pm 0.209$ ; $p = 0.95$ Mean drinks per drinking day: $0.1088 \pm 0.148$ ; $p = 0.46/0.3986 \pm 0.197$ ; <b><math>p = 0.044</math></b> Max. drinks per drinking day: $0.1375 \pm 0.154$ ; $p = 0.37/0.4201 \pm 0.204$ ; <b><math>p = 0.041</math></b>	No. heavy drinking days: $0.0213 \pm 0.012$ ; $p = 0.079$ Mean drinks per drinking day: $0.0183 \pm 0.012$ ; $p = 0.12$ Max. drinks per drinking day: $0.0143 \pm 0.012$ ; $p = 0.24$
<b>Severity of drug abuse</b>				
Grant 2016 (NESARC-III) (N = 36,309)	DSM-V MDD criteria assessed using AUDADIS-V	OR (95% CI) of prevalence of drug use disorder in patients with MDD; 2- year study period assessing lifetime history <sup>d</sup>	<u>12-month drug use disorder</u> Mild drug use disorder: 1.3 (0.98-1.81) Moderate-to-severe drug use disorder: <b>1.3 (1.03-1.76); <math>p &lt; 0.05</math></b> <u>Lifetime drug use disorder</u> Mild drug use disorder: <b>1.3 (1.02-1.53); <math>p &lt; 0.05</math></b> Moderate-to-severe drug use disorder: 1.1 (0.94-1.31)	NR
<b>Impact on alcohol rehabilitation and abstinence</b>				
Suter 2011 (N = 441)	MDD identified using ICD-10 codes	Cumulative probability of abstinence during 1-year follow-up	With vs. without MDD: log-rank $p = NS$ Alcohol use disorder only vs. with clinically significant depressive symptoms: <b>log-rank <math>p &lt; 0.01</math></b> Alcohol use disorder only vs. with clinically significant depressive symptoms at discharge: <b>log-rank <math>p &lt; 0.05</math></b>	NR
<b>Impact on drug rehabilitation and abstinence</b>				
Brenner 2018 (N = 121,669)	NR for MDD; treatment resistant: received $\geq 3$	HR (95% CI) for substance use disorder for treatment-	NR	Any: <b>1.3 (1.2-1.4)</b>

Study	Depression definition	Estimate; time period	Impact of depression on comorbidity	
			Depression prevalence	Depression severity
	treatment episodes within a single depressive episode	resistant depression vs. MDD among patients with prior substance use disorder; mean 4.2-year follow-up <sup>e</sup>		Sedative use: <b>2.9 (2.3-3.7)</b>  Multiple drug use: <b>1.7 (1.5-2.0)</b>
Gerra 2006 (N = 206)	DSM-IV MDD criteria assessed using SCID	Multivariate fitting analysis for patients undergoing a buprenorphine-based rehabilitation program for heroin dependence; 12-month follow-up <sup>f</sup>	<u>Program retention</u> MDD diagnosis vs. buprenorphine doses: 0.64 vs. 0.54 <u>Negative urine metabolites</u> MDD diagnosis vs. buprenorphine doses: 0.68 vs. 0.46	NR
Greenfield 2012 (N = 302)	DSM-IV MDD criteria assessed using SCID	Effect estimate ± SE for effect of depression on change in ADUSE score over treatment period for substance use disorder (mean 25 days) <sup>g</sup>	Main effect of MDD status on Total and Negative Affect ADUSE was NS (data NR)	<u>According to BSI score</u> Total ADUSE score: $\gamma = -0.02 \pm 0.003$ ; <b>p &lt; 0.001</b> ADUSE Negative Affect: $\gamma = -0.02 \pm 0.004$ ; <b>p &lt; 0.001</b>
Landheim 2006 (N = 160)	CIDI, details NR	OR (95% CI) for relapse among alcoholics and poly-substance users; 6-year follow-up <sup>h</sup>	Lifetime MDD: <b>2.1 (1.10-4.51); p = 0.05</b>	NR

Where multiple levels of covariate adjustment were reported, the model with the greatest level of adjustment is reported here. Unless otherwise specified, the effect estimate is for the comparison of depression vs. no depression. Statistically significant differences ( $p < 0.05$ ) are shown in bold font; p-values are reported where available. For the 'Depression recurrence/severity' category, certain studies evaluated the association of certain subtypes of depression such as recurrent

depression or certain severity levels depression on the risk or severity of comorbid disease.

<sup>a</sup> Adjusted for alcohol use at baseline, age, education, financial situation, age of onset of alcohol use, risky single-occasion drinking, and language.

<sup>b</sup> Assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (wave 1); Longitudinal Interval Follow-up Evaluation (subsequent waves).

<sup>c</sup> Adjusted for anxiety disorders, disruptive behavior disorders, and other substance use disorders in adolescence.

<sup>d</sup> Adjusted for age, sex, ethnicity, education, family income, marital status, urbanicity, geographic region, and additional psychiatric comorbidity.

<sup>e</sup> Adjusted for age, sex, area of residence, education level, anxiety disorders, and personality disorders.

<sup>f</sup> Adjusted for age, sex, substance abuse history (years of addiction), psychotropic medication associated to substitution treatment, previous methadone treatment, and residential treatment.

<sup>g</sup> Controlled for intake Inventory of Drug Use Consequences scores, alcohol use disorder diagnosis, and other psychiatric disorders.

<sup>h</sup> Adjusted for age at onset of a substance use disorder.

ADUSE, The Alcohol and Drug Use Self-Efficacy; AUDADIS, Abuse and Alcoholism Alcohol Use Disorder and Associated Disabilities Interview Schedule; BSI, Brief Symptom Inventory; CI, confidence interval; CIDI, Composite International Diagnostic Interview; C-SURF, Cohort Study on Substance Use Risk Factors; DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, hazard ratio; ICD, International Classification of Diseases; Max., maximum; MDD, major depressive disorder; MDI, Major Depression Inventory; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; No., number; NR, not reported; NS, not significant; OR, odds ratio; PHQ, Patient Health Questionnaire; PRISM, Psychiatric Research Interview of Substance and Mood Disorders; SCID, Structured Clinical Interview for DSM-IV disorders; SE, standard error.